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(54) Title: A METHOD FOR THE PROPHYLAXIS AND/OR TREATMENT OF MEDICAL DISORDERS

(57) Abstract: The present invention relates generally to a method for the prophylaxis and/or treatment of skin disorders, and in particular proliferative and/or inflammatory skin disorders, and to genetic molecules useful for same. The present invention is particularly directed to genetic molecules capable of modulating growth factor interaction with its receptor on epidermal keratinocytes to inhibit, reduce or otherwise decrease stimulation of this layer of cells. The present invention contemplates, in a most preferred embodiment, a method for the prophylaxis and/or treatment of psoriasis.

# A METHOD FOR THE PROPHYLAXIS AND/OR TREATMENT OF MEDICAL DISORDERS

## FIELD OF THE INVENTION

The present invention relates generally to a method for the prophylaxis and/or treatment of medical disorders, and in particular proliferative and/or inflammatory skin disorders, and to genetic molecules useful for same. The present invention is particularly directed to genetic molecules capable of modulating growth factor interaction with its receptor on cells such as epidermal keratinocytes to inhibit, reduce or otherwise decrease stimulation of this layer of cells. The present invention contemplates, in a particularly preferred embodiment, a method for the prophylaxis and/or treatment of psoriasis or neovascularization conditions such as neovascularization of the retina. The present invention is further directed to the subject genetic molecules in adjunctive therapy for epidermal hyperplasia, such as in combination with UV treatment, and to facilitate apoptosis of cancer cells and in particular cancer cells comprising keratinocytes.

## BACKGROUND OF THE INVENTION

Bibliographic details of the publications numerically referred to in this specification are collected at the end of the description.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia or any other country.

Psoriasis and other similar conditions are common and often distressing proliferative and/or inflammatory skin disorders affecting or having the potential to affect a significant proportion of the population. The condition arises from over proliferation of basal keratinocytes in the epidermal layer of the skin associated with inflammation in the underlying dermis. Whilst a

range of treatments have been developed, none is completely effective and free of adverse side effects. Although the underlying cause of psoriasis remains elusive, there is some consensus of opinion that the condition arises at least in part from over expression of local growth factors and their interaction with their receptors supporting keratinocyte proliferation *via* keratinocyte receptors which appear to be more abundant during psoriasis.

One important group of growth factors are the dermally-derived insulin-like growth factors (IGFs) which support keratinocyte proliferation. In particular, IGF-I and IGF-II are ubiquitous peptides each with potent mitogenic effects on a broad range of cells. Molecules of the IGF type are also known as "progression factors" promoting "competent" cells through DNA synthesis. The IGFs act through a common receptor known as the Type I or IGF-I receptor, which is tyrosine kinase linked. They are synthesised in mesenchymal tissues, including the dermis, and act on adjacent cells of mesodermal, endodermal or ectodermal origin. The regulation of their synthesis involves growth hormone (GH) in the liver, but is poorly defined in most tissues [1].

Particular proteins, referred to as IGF binding proteins (IGFBPs), appear to be involved in autocrine/paracrine regulation of tissue IGF availability [2]. Six IGFBPs have so far been identified. The exact effects of the IGFBPs is not clear and observed effects *in vitro* have been inhibitory or stimulatory depending on the experimental method employed [3]. There is some evidence, however, that certain IGFBPs are involved in targeting IGF-I to its cell surface receptor.

Skin, comprising epidermis and underlying dermis, has GH receptors on dermal fibroblasts [4]. Fibroblasts synthesize IGF-I as well as IGFBPs-3, -4, -5 and -6 [5] which may be involved in targeting IGF-I to adjacent cells as well as to the overlaying epidermis. The major epidermal cell type, the keratinocyte, does not synthesize IGF-I, but possesses IGF-I receptors and is responsive to IGF-I [6].

It is apparent, therefore, that IGF-I and other growth promoting molecules, are responsible for or at least participate in a range of skin cell activities. In accordance with the present invention, the inventors have established that aberrations in the normal functioning of these molecules or

aberrations in their interaction with their receptors is an important factor in a variety of medical disorders such as proliferative and/or inflammatory skin disorders. It is proposed, therefore, to target these molecules or other molecules which facilitate their functioning or interaction with their receptors to thereby ameliorate the effects of aberrant activity during or leading to skin disease conditions and other medical conditions such as those involving neovascularization. Furthermore, these molecules may also be used to facilitate apoptosis of target cells and may be useful as adjunctive therapy for epidermal hyperplasia.

## SUMMARY OF THE INVENTION

Nucleotide and amino acid sequences are referred to by a sequence identifier, i.e. (<400>1), (<400>2), etc. A sequence listing is provided after the claims.

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

Accordingly, one aspect of the present invention contemplates a method for ameliorating the effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a mammal, said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation or a cell otherwise involved in the said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing a growth factor mediated cell proliferation and/or inflammation and/or other medical disorder.

According to this preferred embodiment, there is provided a method for ameliorating the effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a mammal, said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation or a cell otherwise involved with said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof

capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or inflammation and/or other medical disorder.

According to this embodiment, there is provided a method for ameliorating the effects of a proliferative and/or inflammatory skin disorder such as psoriasis said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation with effective amounts of UV treatment and a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or inflammation.

According to this embodiment, there is provided in a particularly preferred aspect a ribozyme comprising a hybridising region and a catalytic region wherein the hybridising region is capable of hybridising to at least part of a target mRNA sequence transcribed from a genomic gene corresponding to <400>1 or <400>2 wherein said catalytic domain is capable of cleaving said target mRNA sequence to reduce or inhibit IGF-I mediated cell proliferation and/or inflammation and/or other medical disorders.

Yet another aspect of the present invention contemplates co-suppression to reduce expression or to inhibit translation of an endogenous gene encoding, for example, IGF-I, its receptor, or IGFBPs such as IGFBP-2 and/or -3. In co-suppression, a second copy of an endogenous gene or a substantially similar copy or analogue of an endogenous gene is introduced into a cell following topical administration. As with antisense molecules, nucleic acid molecules defining a ribozyme or nucleic acid molecules useful in co-suppression may first be protected such as by using a nonionic backbone.

Another aspect of the present invention contemplates a pharmaceutical composition for topical administration which comprises a nucleic acid molecule capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation such as psoriasis and one or more pharmaceutically acceptable carriers and/or diluents.

Yet another aspect of the present invention contemplates the use of a nucleic acid molecule in the manufacture of a medicament for the treatment of proliferative and/or inflammatory skin disorders or other medical disorders mediated by a growth factor.

Still a further aspect of the present invention contemplates an agent comprising a nucleic acid molecule as hereinbefore defined useful in the treatment of proliferative and/or inflammatory skin disorders, such as psoriasis or other medical disorder..

The present invention further contemplates the use of the genetic molecules and in particular the antisense molecules to inhibit the anti-apoptotic activity of IGF-I receptor.

## BRIEF DESCRIPTION OF THE FIGURES

**Figure 1** is a representation of the nucleotide sequence of IGFBP-2.

```
LOCUS       HSIGFBP2     1433 bp    RNA             PRI       31-JAN-1990
DEFINITION  Human mRNA for insulin-like growth factor binding protein (IGFBP-2)
ACCESSION   X16302
KEYWORDS    insulin-like growth factor binding protein.
SOURCE      human
  ORGANISM  Homo sapiens
            Eukaryota; Animalia; Metazoa; Chordata; Vertebrata; Mammalia;
            Theria; Eutheria; Primates; Haplorhini; Catarrhini; Hominidae.
REFERENCE   1  (bases 1 to 1433)
  AUTHORS   Binkert,C., Landwehr,J., Mary,J.L., Schwander,J. and Heinrich,G.
  TITLE     Cloning, sequence analysis and expression of a cDNA encoding a
            novel insulin-like growth factor binding protein (IGFBP-2)
  JOURNAL   EMBO J. 8, 2497-2502 (1989)
  STANDARD  full automatic
COMMENT     NCBI gi: 33009
FEATURES             Location/Qualifiers
     source          1. .1433
                     /organism="Homo sapiens"
                     /dev_stage="fetal"
                     /tissue_type="liver"
     misc_feature    1416. .1420
                     /note="pot. polyadenylation signal"
     polyA_site      1433
                     /note="polyadenylation site"
     CDS             118. .1104
                     /note="precursor polypeptide;  (AA -39 to 289);  NCBI gi:
                     33010."
                     /codon_start=1
                     /translation="MLPRVGCPALPLPPPPLLPLLPLLLLLLGASGGGGGARAEVLFR
                     CPPCTPERLAACGPPPVAPPAAVAAVAGGARMPCAELVREPGCGCCSVCARLEGEACG
                     VYTPRCGQGLRCYPHPGSELPLQALVMGEGTCEKRRDAEYGASPEQVADNGDDHSEGG
                     LVENHVDSTMNMLGGGGSAGRKPLKSGMKELAVFREKVTEQHRQMGKGGKHHLGLEEP
                     KKLRPPPARTPCQQELDQVLERISTMRLPDERGPLEHLYSLHIPNCDKHGLYNLKQCK
                     MSLNGQRGECWCVNPNTGKLIQGAPTIRGDPECHLFYNEQQEACGVHTQRMQ"
                     (<400>21)
     CDS             118. .234
                     /note="signal peptide;  (AA -39 to -1);  NCBI gi: 33011."
                     /codon_start=1
                     /translation="MLPRVGCPALPLPPPPLLPLLPLLLLLLGASGGGGGARA"
                     (<400>22)
     CDS             235. .1101
                     /note="mature IGFBP-2;  (AA 1 to 289);  NCBI gi: 33012."
                     /codon_start=1
                     /translation="EVLFRCPPCTPERLAACGPPPVAPPAAVAAVAGGARMPCAELVR
                     EPGCGCCSVCARLEGEACGVYTPRCGQGLRCYPHPGSELPLQALVMGEGTCEKRRDAE
                     YGASPEQVADNGDDHSEGGLVENHVDSTMNMLGGGGSAGRKPLKSGMKELAVFREKVT
                     EQHRQMGKGGKHHLGLEEPKKLRPPPARTPCQQELDQVLERISTMRLPDERGPLEHLY
                     SLHIPNCDKHGLYNLKQCKMSLNGQRGECWCVNPNTGKLIQGAPTIRGDPECHLFYNE
                     QQEACGVHTQRMQ" (<400>23)
BASE COUNT      239 a    466 c    501 g    227 t
ORIGIN
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```
HSIGFBP2  Length: 1433  May 11, 1994  10:06  Type: N  Check: 6232  ..
```

**Figure 2** is a representation of the nucleotide sequence of IGFBP-3.

```
LOCUS       HUMGFIBPA    2474 bp ss-mRNA            PRI       15-JUN-1990
DEFINITION  Human growth hormone-dependent insulin-like growth factor-binding
            protein mRNA, complete cds.
ACCESSION   M31159
KEYWORDS    insulin-like growth factor binding protein.
SOURCE      Human plasma, cDNA to mRNA, clone BP-53.
  ORGANISM  Homo sapiens
            Eukaryota; Animalia; Chordata; Vertebrata; Mammalia; Theria;
            Eutheria; Primates; Haplorhini; Catarrhini; Hominidae.
REFERENCE   1  (bases 1 to 2474)
  AUTHORS   Wood,W.I., Cachianes,G., Henzel,W.J., Winslow,G.A., Spencer,S.A.,
            Hellmiss,R., Martin,J.L. and Baxter,R.C.
  TITLE     Cloning and expression of the growth hormone-dependent insulin-like
            growth factor-binding protein
  JOURNAL   Mol. Endocrinol. 2, 1176-1185 (1988)
  STANDARD  full automatic
COMMENT     NCBI gi: 183115
FEATURES             Location/Qualifiers
     mRNA            <1. .2474
                     /note="GFIBP mRNA"
     CDS             110. .985
                     /gene="IGFBP1"
                     /note="insulin-like growth factor-binding protein;  NCBI
                     gi: 183116."
                     /codon_start=1
                     /translation="MQRARPTLWAAALTLLVLLRGPPVARAGASSGGLGPVVRCEPCD
                     ARALAQCAPPPAVCAELVREPGCGCCLTCALSEGQPCGIYTERCGSGLRCQPSPDEAR
                     PLQALLDGRGLCVNASAVSRLRAYLLPAPPAPGNASESEEDRSAGSVESPSVSSTHRV
                     SDPKFHPLHSKIIIIKKGHAKDSQRYKVDYESQSTDTQNFSSESKRETEYGPCRREME
                     DTLNHLKFLNVLSPRGVHIPNCDKKGFYKKKQCRPSKGRKRGFCWCVDKYGQPLPGYT
                     TKGKEDVHCYSMQSK" (<400>24>)
     source          1. .2474
                     /organism="Homo sapiens"
BASE COUNT      597 a    646 c    651 g    580 t
ORIGIN
```

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HUMGFIBPA  Length: 2474  May 11, 1994  10:00  Type: N  Check: 9946  ..
```

**Figure 3** is a representation of the nucleotide sequence of IGF-1-receptor.

```
LOCUS       HSIGFIRR     4989 bp    RNA             PRI       28-MAR-1991
DEFINITION  Human mRNA for insulin-like growth factor I receptor
ACCESSION   X04434 M24599
KEYWORDS    glycoprotein; insulin receptor;
            insulin-like growth factor I receptor; membrane glycoprotein;
            receptor; tyrosine kinase.
SOURCE      human
```

```
  ORGANISM  Homo sapiens
            Eukaryota; Animalia; Metazoa; Chordata; Vertebrata; Mammalia;
            Theria; Eutheria; Primates; Haplorhini; Catarrhini; Hominidae.
REFERENCE   1  (bases 1 to 4989)
  AUTHORS   Ullrich,A., Gray,A., Tam,A.W., Yang-Feng,T., Tsubokawa,M.,
            Collins,C., Henzel,W., Bon,T.L., Kathuria,S., Chen,E., Jakobs,S.,
            Francke,U., Ramachandran,J. and Fujita-Yamaguchi,Y.
  TITLE     Insulin-like growth factor I receptor primary structure: comparison
            with insulin receptor suggests structural dererminants that define
            functional specificity
  JOURNAL   EMBO J. 5, 2503-2512 (1986)
  STANDARD  full automatic
COMMENT     NCBI gi: 33058
FEATURES             Location/Qualifiers
     source          1. .4989
                     /organism="Homo sapiens"
                     /tissue_type="placenta"
                     /clone_lib="(lamda)gt10"
                     /clone="(lambda)IGF-1-R.85, (lambda)IGF-1-R.76"
     sig_peptide     32. .121
     mat_peptide     122. .4132
                     /note="IGF-I receptor"
     misc_feature    122. .2251
                     /note="alpha-subunit (AA 1 - 710)"
     misc_feature    182. .190
                     /note="pot.N-linked glycosylation site (AA 21 - 23)"
     misc_feature    335. .343
                     /note="pot.N-linked glycostlation site (AA 72 - 74)"
     misc_feature    434. .442
                     /note="pot.N-linked glycostlation site (AA 105 - 107)"
     misc_feature    761. .769
                     /note="pot.N-linked glycostlation site (AA 214 - 216)"
     misc_feature    971. .979
                     /note="pot.N-linked glycostlation site (AA 284 - 286)"
     misc_feature    1280. .1288
                     /note="pot.N-linked glycostlation site (AA 387 - 389)"
     misc_feature    1343. .1351
                     /note="pot.N-linked glycosylation site (AA 408 - 410)"
     misc_feature    1631. .1639
                     /note="pot.N-linked glycostlation site (AA 504 - 506)"
     misc_feature    1850. .1858
                     /note="pot.N-linked glycosylation site (AA 577 - 579)"
     misc_feature    1895. .1903
                     /note="pot.N-linked glycosylation site (AA 592 - 594)"
     misc_feature    1949. .1957
                     /note="pot.N-linked glycosylation site (AA 610 - 612)"
     misc_feature    2240. .2251
                     /note="putative proreceptor processing site (AA 707 -
                     710)"
     misc_feature    2252. .4132
                     /note="beta-subunit (AA 711 - 1337)"
     misc_feature    2270. .2278
                     /note="pot.N-linked glycosylation site (AA 717 - 719]"
     misc_feature    2297. .2305
                     /note="pot.N-linked glycosylation site (AA 726 - 728)"
     misc_feature    2321. .2329
                     /note="pot.N-linked glycosylation site (AA 734 - 736)"
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     misc_feature    2729. .2737
                     /note="pot.N-linked glycosylation site (AA 870 - 872)"
     misc_feature    2768. .2776
                     /note="pot.N-linked glycosylation site (AA 883 - 885)"
     misc_feature    2837. .2908
                     /note="transmembrane region (AA 906 - 929)"
     misc_feature    2918. .2926
                     /note="pot.N-linked glycosylation site (AA 933 - 935)"
     misc_feature    3047. .3049
                     /note="pot.ATP binding site (AA 976)"
     misc_feature    3053. .3055
                     /note="pot.ATP binding site (AA 978)"
     misc_feature    3062. .3064
                     /note="pot.ATP binding site (AA 981)"
     misc_feature    3128. .3130
                     /note="pot.ATP binding site (AA 1003)"
     CDS             32. .4132
                     /product="IGF-I receptor"
                     /note="50 stops when translation attempted, frame 1, code
                     0"
BASE COUNT     1216 a   1371 c   1320 g   1082 t
ORIGIN

  HSIGFIRR  Length: 4989  May 11, 1994  12:10  Type: N  Check: 133  ..
```

**Figure 4A** is a photographic representation of a Western ligand blot of HaCaT conditioned medium showing IGFBP-3 secreted in 24 hours after 7 day treatment with phosphorothioate oligonucleotides (BP3AS2, BP3AS3 and BP3S) at 0.5$\mu$M and 5$\mu$M;
* no oligonucleotide added.

**Figure 4B** is a graphical representation of a scanning imaging desitometry of Western ligand blot (Figure 4A), showing relative band intensities of IGFBP-3 and the 24kDa IGFBP-4 after treatment with phosphorothioate oligonucleotides;
* no oligonucleotide added.

**Figure 5A** is a photographic representation of a Western ligand blot of HaCaT conditioned medium showing IGFBP-3 secreted in 24 hours after 7 day treatment with phosophorothioate oligonucleotide BP3AS2 at 0.5$\mu$M compared with several control oligonucleotides at 0.5$\mu$M. (a) oligonucleotide BP3AS2NS; (b) oligonucleotide BP3AS4; (c) oligonucleotide BP3AS4NS; and (untreated), no oligonucleotide added.

**Figure 5B** is a graphical representation of a scanning imaging densitometry of Western ligand blot (Figure 5A), showing relative band intensities of IGFBP-3 after treatment with phosphorothioate oligonucleotides as in Figure 5A, showing IGFBP-3 band intensities expressed as a percentage of the average band intensity from conditioned medium of cells not treated with oligonucleotide.

**Figure 6** is a graphical representation showing inhibition of IGF-I binding by antisense oligonucleotides to IGF-I receptor. IGFR.AS: antisense; IGFR.S: sense.

**Figure 7** is a graphical representation showing inhibition of IGFBP-3 production in culture medium following initial treatment with antisense oligonucleotides once daily over a 2 day period.

**Figure 8** is a graphical representation showing optimization of IGFBP-3 antisense oligonucleotide concentration as determined by relative IGFBP-3 concentration in culture medium.

**Figure 9** is a diagramatic representation of a map of IGF-1 Receptor mRNA and position of target ODNs.

**Figure 10** is a photographical representation showing Lipid-mediated uptake of oligonucleotide in keratinocytes. HaCaT keratinocytes were incubated for 24 hours in medium (DMEM plus 10% v/v FCS) containing fluorescently labelled ODN (R451, 30 nM) and cytofectin GSV (2 $\mu$g/ml). The cells were then transferred to ODN-free medium and fluorescence microscopy (a) and phase contrast (b) images of the cells were obtained.

**Figure 11** is a graphical representation of uptake (A) and toxicity (B) of ODN/lipid complexes in keratinocytes. Confluence HaCaT keratinocytes were incubated in DMEM containing fluoresently labelled ODN (R451) plus liposome over 120 hours, viewed using fluorescene microscopy and trypan blue stained and counted.

**Figure 12** is a graphical representation of an IGF-1 Receptor mRNA in ODN treated (30nM) HaCaT cells (2$\mu$g/ml GSV). HaCaT keratinocytes were treated for 96 hours with C-5 propynyl, dU, dC ODNs complexed with cytofectin GSV. Cells were treated with ODNs complementary to the human IGF-I receptor mRNA (27, 32, 74 and 78), 2 randomised sequence ODNs (R451) and R766), liposome alone (GSV) or were left untreated (UT). Total RNA was isolated then analysed for IGF-I receptor mRNA and GAPDH mRNA levels by RNase Protection and PhosphorImager quantitiation.

(A) Electrophoretic analysis of IGF-I receptor and GAPDH mRNA fragments after RNase Protection. Molecular weight markers are shown on the right hand side. Full length probe is shown on the left hand side (G-probe and I-probe). GAPDH protected fragments (G) are seen at 316 bases and IGF-I receptor protected fragments (I) are seen at 276 bases.

(B) Relative level of IGF-I receptor mRNA following each treatment is shown.

**Figure 13** is a graphical representation of an IGF-1 receptor mRNA in ODN treated (30nM) HaCaT cells (2$\mu$g/ml GSV). Summary of IGF-I receptor ODN screening data. HaCaT keratinocytes were treated for 96 hours with C-5 propynyl, dU, dC ODNs complexed with cytofectin GSV. Total RNA was isolated then analysed for IGF-I receptor mRNA and GAPDH mRNA levels by RNase protection and phosphorImager quantitiation. Relative level of IGF-I receptor mRNA is shown after treatment with ODNs complementary to the human IGF-I receptor mRNA, 4 randomised sequence ODNs and liposome alone. (26-86=IGF-I receptor ODNs; R1, R4, R7 and R9 = randomised ODNs (R1=R121, R4=R451, R7=R766, R9=R961); GSV=liposome alone; UT=untreated). *indicates a significant difference in relative IGF-I receptor mRNA from GSV treated cells ($n=4$-10, $p<0.05$).

**Figure 14** is a graphical representation of the effect of antisense oligonucleotides on IGF-1 receptor levels on the surface of keratinocytes. HaCaT cells were grown to confluence in 24-well plates in DMEM containing 10% v/v FCS. Oligodeoxynucleotide (ODN) and Cytofectin GSV (GSV, Glen Research) were mixed together in serum-free DMEM, incubated at room

temperature for 10 minutes before being diluted ten-fold in medium and placed on the cells. Cells were incubated for 72 hours with 30 nM random sequence or antisense ODN and 2 $\mu$g/ml GSV or with GSV alone in DMEM containing 10% v/v FCS with solutions replaced every 24 hours. This was followed by incubation with ODN/GSV in serum-free DMEM for 48 hours. All incubations were performed at 37°C. Wells were washed twice with 1 ml cold PBS. Serum-free DMEM containing $10^{-10}$M $^{125}$I-IGF-I was added with or without the IGF-I analogue, des (1-3) IGF-I, at $10^{-10}$M to $10^{-7}$M. Cells were incubated at 4°C for 17 hours with gentle shaking then washed three times with 1 ml cold PBS and lysed in 250 $\mu$l 0.5M NaOH/0.1% v/v Triton X-100 at room temperature for 4 hours. Specific binding of the solubilised cell extract was measured using a $\gamma$ counter.

**Figure 15** is a graphical representation of the effect of antisense oligonucleotides on IGF-1 receptor levels on the surface of keratinocytes.

**Figure 16** is a photographical representation of H & E stained sections of (A) psoriatic skin biopsy prior to grafting and (B) 49 day old psoriatic skin graft using skin from the same donor.

**Figure 17** is a photographical representation of uptake of oligonucleotide after intradermal injection into psoriatic skin graft on a nude mouse. Psoriatic skin graft was intradermally injected with ODN (R451, 50 $\mu$l, 10 $\mu$M). The graft was removed and sectioned after 24 hours, then viewed using confocal microscopy.

**Figure 18(a)** is a photographical representation of Pregraft, Donor JH, Donor JH, PBS treated, 50$\mu$l, Donor JH, #50 treated, 50$\mu$l, 10$\mu$M.

**Figure 18(b)** is a photographical representation of Donor LB, pregraft, Donor LB, PBS treated (50$\mu$l), Donor LB, #74 treated (50$\mu$l, 10$\mu$M).

**Figure 18(c)** is a photographical representation of Donor PW, pregraft, Donor PW, R451 treated (50$\mu$l, 10$\mu$M), Donor LB, #74 treated (50$\mu$l, 10$\mu$M).

**Figure 18(d)** is a photographical representation of Donor GM, pregraft, Donor GB, R451 treated (50$\mu$l, 10$\mu$M), Donor GM, #27 treated (50$\mu$l, 10$\mu$M).

**Figure 19(a)** is a photographical representation showing Donor JH pregraft, Donor JH PBS treated 50$\mu$l, Donor JH #50 treated 50$\mu$l, 10$\mu$M.

**Figure 19(b)** is a photographical representation Donor LB pregraft, Donor LB PBS treated 50$\mu$l, Donor LB #74 treated 50$\mu$l, 10$\mu$M.

**Figure 19(c)** is a photographical representational showing Donor PW pregraft, Donor PW r451 treated 50$\mu$l, 10$\mu$M, Donor PW #74 treated 50$\mu$l, 10$\mu$M.

**Figure 19(d)** is a photographical representation showing Donor GM pregraft, Donor GM R451 treated 50$\mu$l, 10$\mu$M, Donor #27 treated 50$\mu$l, 10$\mu$M.

**Figure 20** is a graphical representation showing suppression of psoriasis after treatment with oligonucleotide (quantification). Oligonucleotide (50 $\mu$l, 10$\mu$M) was injected every two days for 20 days, as were control treatments. Skin thickness was measured by removing the skin and using computer software (MCID analysis) to measure the exact thickness of each graft. N=3-4 for each treatment. *indicates a significant difference from the pregraft value (ANOVA, $P<0.05$)

**Figure 21** is a photographic representation of αhKi-67 imunobiological binding.

**Figure 22** is a photographical representation showing penetration of oligonucleotide into human skin after topical treatment. Fluorescently labelled oligonucleotide (10 $\mu$M R451) was

applied topically after formulation with cytofectin GSV (10 $\mu$g/ml) and viewed using confocal microscopy.

**Figure 23** is a photographical representation showing penetration of oligonucleotide into human skin after application of topical gel formation. Fluorescently labelled oligonucleotide (10 $\mu$M R451) was applied topically after complexing with cytofectin GSV (10 $\mu$g/ml) and formulation into 3% methylcellulose gel. Image was obtained using confocal microscopy.

**Figure 24** is a graphical representation showing IGFBP-3 mRNA.

**Figure 25(a)** is a graphical representation showing IGFBP-3 mRNA in AON treated (100nM) HaCaT cells (2$\mu$g/ml GSV).

**Figure 25(b)** is a graphical representation showing IGFBP-3 mRNA levels of AON treated (100nm) HaCaT cells (2$\mu$g/ml GSV).

**Figure 25(c)** is a graphical representation showing IGFBP-3 mRNA in AON treated (30nM) HaCaT cells (2$\mu$g/ml GSV).

**Figure 25(d)** is a graphical representation showing IGFBP-3 mRNA in AON treated (30nM) HaCaT cells (2$\mu$g/ml GSV).

**Figure 26(a)** is a graphical representation showing IGFBP-3 mRNA in ODN treated (30nM) HaCaT cells (2$\mu$g/ml). HaCaT keratinocytes were treated for 51 hours with C-5 propynl, dU, dC ODNs complexed with cytofectin GSV. Total RNA was isolated then analysed for IGFBP-3 mRNA and GAPDH mRNA levels by Northern analysis and phosphorimager quantitation. Relative level of IGFBP-3 mRNA is shown after treatment with ODNs complementary to the human IGFBP-3 mRNA, 4 randomised sequence ODNs and lipsome alone. (1-24=IGFBP-3 ODNs; R1, R4, R7 and R9=randomised ODNs (R1=R121, R4=R451, R7=R766, R9 R961); GS=liposome alone; UT=untreated). *indicates a significant different in relative

IGFBP-3 mRNA from GSV treated cells (n- 5-8, $p<0.01$), **indicates a significant difference in relative IGFBP-3 mRNA from GSV treated cells (n= 5-8, $p<0.05$).

**Figure 26(b)** is a graphical representation showing IGFBP-3 mRNA in ODN treated (100nM) HaCaT cells (2$\mu$g/ml GSV). HaCaT keratinocytes were treated for 51 hours with C-5 propynl, dU, dC ODNs complexed with cytofectin GSV. Total RNA was isolated then analysed for IGFBP-3 mRNA and GAPDH mRNA levels by Northern analysis and phosphorimager quantitation. Relative level of IGFBP-3 mRNA is shown after treatment with ODNs complementary to the human IGFBP-3 mRNA, 4 randomised sequence ODNs and liposome alone.. (1-24=IGFBP-3 ODNs; R1, R4, R7 and R9 = randomised ODNs (R1-R121, R4=R451, R7=R766, R9-R961), GS=lipsome alone; UT=untreated). *indicates a significant difference in relative IGFBP-3 mRNA from GSV treated cells (n- 6-8, $p<0.01$).

**Figure 27** is a representation showing a reduction in IGF-I receptor mRNA in HaCaT cells following treatment with antisense oligonucleotides. Confluent HaCaT cells were treated every 24 h for 4 days with 2 $\mu$g/ml GSV lipid alone (GSV) or complexed with 30 nM IGF-I receptor specific oligonucleotides *(#26 to #86)* or random sequence oligonucleotides (R121, R451 and R766). Total RNA was isolated and analysed for IGF-I receptor and GAPDH mRNA by RNase protection assay. **(a)**. Representative RNase protection assay gel showing IGF-I receptor *(IGF*R) and GAPDH mRNA in untreated or treated HaCaT cells. In this example, a reduction in IGFR band intensity relative to GAPDH can be seen with AON #27 and #78, but not with #32, #74 or the controls *(R*4, *R*7, random oligonucleotides R451 and R766, respectively; G, GSV lipid; *UT*, untreated).

**(b)** Densitometric quantitation of IGF-I receptor mRNA (normalised to GAPDH mRNA) in HaCaT cells following treatment with IGF-I receptor specific oligonucleotides (solid black), random sequence oligonucleotides (horizontal striped bar) or GSV alone (shaded bar) compared to untreated cells *(UT*, vertical striped bar). Each oligonucleotide was assayed in duplicate in at least two separate experiments.

Results are presented as mean ± SEM. A one-way ANOVA followed by Tukey's (▲) test was performed; ▲ indicates a significant difference between cells treated with IGF-I receptor specific AONs and all of the control treatments ($p<0.05$). n=4 except for #27 and #32 (n=6), #28 and #68 (n=3), R766 (n=9), and R451, GSV and untreated (n=10).

**Figure 28** is a representation showing a reduction in total cellular IGF-I receptor protein following antisense oligonucleotide treatment. Confluent HaCaT cells were treated every 24 h for 4 days with 2 μg/ml GSV lipid alone (GSV) or complexed with 30 nM IGF-I receptor specific AONs (#27, #50 and #64) or the random sequence oligonucleotide, R451. Total cellular protein was isolated and analysed for IGF-I receptor by SDS PAGE followed by western blotting with an antibody specific for the human IGF-I receptor. (a) Duplicate treated cellular extracts showing the IGF-I receptor at the predicted size of 110 kD

(b) Densitometric quantitation of IGF-I receptor protein. Results are presented as mean ± SEM of four different experiments each performed in duplicate. A one-way ANOVA followed by a Dunnett's test was performed; * indicates a significant difference from GSV treated cells ($p<0.01$). *GSV*, GSV lipid alone; *UT*, untreated; R451, random sequence oligonucleotide; *64*, *50*, *27*, IGF-I receptor-specific AONs.

**Figure 29** is a representation showing a reduction in IGF-I receptor numbers on the keratinocyte cell surface after antisense oligonucleotide treatment. HaCaT cells were transfected with IGF-I receptor specific AONs #27 (—▲—), #50 (—x—), #64 (--■--), a random sequence oligonucleotide R451 (—o—), or treated with GSV lipid alone (--□—) every 24 h for four days (untreated cells, --✳--). Competition binding assays using $^{125}$I-IGF-I and the receptor-specific analogue, des(1-3)IGF-I, were performed (inset); plotted values are means ± standard error. The mean values were then subjected to Scatchard analysis.

**Figure 30** is a representation showing a reduction in keratinocyte cell number following antisense oligonucleotide treatment. HaCaT cells, initially at 40% confluence, were transfected with the IGF-I receptor specific AON #64, control sequences R451 and 6416, or

treated with GSV lipid alone every 24 h for 2 days (UT, untreated cells). Cell number was measured in the culture wells using a dye binding assay (Experimental protocol). Results are presented as mean ± SD. A one-way ANOVA was performed, followed by a Tukey's multiple comparison test. ▲ indicates a significant difference between cells treated with AON #64 and all of the control treatments ($p < 0.001$).

**Figure 31** is a representation showing a reversal of epidermal hyperplasia in psoriatic human skin grafts on nude mice following intradermal injection with antisense oligonucleotides

Grafted psoriasis lesions were injected with IGF-I receptor specific AONs, a random sequence oligonucleotide in PBS, or with PBS alone, every 2 days for 20 days, then analysed histologically. **(a)** Donor A graft treated with AON #50 showing epidermal thinning compared with pregraft and control *(PBS)* treated graft, and Donor B graft treated with AON #27 showing epidermal thinning compared with pregraft and control (R451) treated graft. E, epidermis; *Scale bar*, 400 mm; all pictures are at the same magnification. **(b)** Mean epidermal cross-sectional area over the full width of grafts was determined by digital image analysis. Results are presented as mean ± SEM. *Shaded bars*, control treatments: R451, random oligonucleotide sequence; *solid bars*, treatments with oligonucleotides that inhibited IGF-I receptor expression in vitro. * indicates a significant difference from the vehicle treated graft ($p < 0.01$, $n = 5$-7), ++ indicates a significant difference from the random sequence (R451) treated graft ($p < 0.01$, $n = 5$-7). **(c)** Parakeratosis *(arrow)* was absent in grafts treated with IGF-I receptor AONs *(AON #50)* but persisted in pregraft and control *(PBS)* treated graft. *Scale bar, 100 mm.*

**Figure 32** is a representation showing a reversal of epidermal hyperplasia correlates with reduced IGF-I receptor mRNA in grafted psoriasis lesions treated with antisense oligonucleotides (a) A psoriasis lesion prior to grafting, and after grafting and treatment with IGF-I receptor specific oligonucleotide *#27 (AON #27)* or random sequence *(R451)* was immunostained with antibodies to Ki67 to identify proliferating cells. Proliferating cells are indicated by a dark brown nucleus (arrows). *Scale bar, 250 mm*; all pictures are at the same

magnification. **(b)** The same lesion prior to grafting and after oligonucleotide treatment as in (a) was subjected to in situ hybridisation with a $^{35}$S-labeled cRNA probe complementary to the human IGF-I receptor mRNA. The presence of IGF-I receptor mRNA is indicated by silver grains (tiny black speckles), which are almost eliminated in the epidermis of the lesion treated with the IGF-I receptor-specific oligonucleotide #27 (AON #27). Arrows indicate the basal layer of the epidermis with dermis underneath. *Scale bar, 50 μm.*

**Figure 33** is a representation showing a reduction in IGF-I receptor mRNA in HaCaT keratinocytes following treatment with oligonucleotides. HaCaT cell monolayers grown to 90% confluence in DMEM contianing 10% v/v fetal calf serum were treated with 24 h for two days with 2 μg/ml GSV lipid alone (GSV) or complexed with 30 nM oligonucleotide. Total RNA was isolated and analysed for IGF-I receptor and GAPDH mRNA using a commercially availble ribonuclease protection assay kit (RPAII, Ambicon Inc, Austin, Texas). Band intensity was quantified using ImageQuant software (Molecular Dynamics, Sunnyvale, California).

**Figure 34** is a representation showing a reduction in IGF-I receptor protein in HaCaT keratinocytes following treatment with oligonucleotides. HaCaT cell monolayers grown to 90% confluence in DMEM containing 10% v/v fetal calf serum were treated every 24 h for four days with 2 μg/ml GSV lipid alone (GSV) or complexed with 30 nM oligonucleotide. Cells were lyased in a buffer containing 50 mM HEPES, 150 mM NaCl, 10% v/v gycerol, 1% v/v Triton X-100 and 100 μg/ml aprotinin on ice for 30 mins, then 30 μg of lysate was loaded onto a denaturing 7% w/v polyacrylamide gel followed by transfer onto an Immobilon-P membrane (Millipore, Bedford, Massachusetts). Membranes were incubated with the anti-IGF-I receptor antibody C20 (Sanra Cruz Biotechnology Inc., Santa Cruz, California, 25 ng/ml in 150 mM NaCl, 10 mM Tris-HCl, pH 7.4, 0.1% v/v Tween 20) for 1 h at room temperature and developed using the Vistra ECF western blotting kit (Amersham, Buckinghamshire, England). Band intensity was quantified using ImageQuant software (Molecular Dynamics, Sunnyvale, California).

**Figure 35** is a representation showing a reduction in HaCaT keratinocyte cell number following treatment with oligonucleotides. HaCaT cell monolayers grown to 40% confluence in DMEM containing 10% fetal calf serum were treated every 24 h for three days with 2 $\mu$g/ml GSV lipid alone (GSV) or complexed with 15 nM oligonucleotide. Cell number was measured every 24 h using the amido black dye binding assay [32].

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is predicated in part on the use of molecules and in particular genetic molecules and more particularly antisense molecules to down-regulate a growth factor, its receptor and/or growth factor expression facilitating sequences.

Accordingly, one aspect of the present invention contemplates a method for ameliorating the effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a mammal, said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation or a cell otherwise involved in the said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing a growth factor mediated cell proliferation and/or inflammation and/or other medical disorder.

Growth factor mediated cell proliferation and inflammation are also referred to as epidermal hyperplasias and these and other medical disorders may be mediated by any number of molecules such as but not limited to IGF-I, keratinocyte growth factor (KGF), transforming growth factor-α (TGFα), tumour necrosis factor-α (TNFα), interleukin-1, -4, -6 and 8 (IL-1, IL-4, IL-6 and IL-8, respectively), basic fibroblast growth factor (bFGF) or a combination of one or more of the above. The present invention is particularly described and exemplified with reference to IGF-I and its receptor (IGF-I receptor) and to IGF-I facilitating molecules, IGFBPs, since targeting these molecules according to the methods contemplated herein provides the best results to date. This is done, however, with the understanding that the present invention extends to any growth factor or cytokine-like molecule, a receptor thereof or a facilitating molecule like the IGFBPs involved in skin cell proliferation such as those molecules contemplated above and/or their receptors and/or facilitating molecules therefor.

According to this preferred embodiment, there is provided a method for ameliorating the effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a mammal, said method comprising contacting the proliferating and/or inflamed skin or skin

capable of proliferation and/or inflammation or a cell otherwise involved with said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or inflammation and/or other medical disorder.

The present invention is particularly described by psoriasis as the proliferative skin disorder. However, the subject invention extends to a range of proliferative and/or inflammatory skin disorders or epidermal hyperplasias such as but not limited to psoriasis, ichthyosis, pityriasis rubra pilaris ("PRP"), seborrhoea, keloids, keratoses, neoplasias and scleroderma, warts, benign growths and cancers of the skin. The present invention extends to a range of other disorders such as neovascularization conditions such as but not limited to hyperneovasularization such as neovascularization of the retina, lining of the brain, skin, hyperproliferation of the inside of blood vessels, kidney disease, atherosclerotic disease, hyperplasias of the gut epithelium or growth factor mediated malignancies such as IGF1-mediated malignancies.

Furthermore, down-regulation of IGF-I receptor is useful as adjunctive therapy for epidermal hyperplasia. In accordance with this aspect of the present invention it is known that IGF-I receptor elicits separate intracellular signals which prevent apoptosis [19]. In keratinocytes, IGF-I receptor activation has been shown to protect UV-irradiated cells from apoptosis [20]. In another cell type, a number of IGF-I receptors expressed by the cells correlated with tumorigenicity and apoptotic resistance [21]. Consequently, in accordance with the present invention, by inactivating IGF-I receptor on cells such as epidermal keratinocytes will achieve three important outcomes:

(i) Acute epidermal hyperplasia following UV has been suggested to increase the risk of keratinocyte carcinogenic transformation [22]. By reducing IGF-I receptor expression in the epidermis, the incidence of epidermal hyperplasia following UV exposure is likely to be reduced leading to an overall acceleration in normalization of the lesion and reduced carcinogenic risk.

(ii) Inhibition of anti-apoptotic action of IGF-I receptor will enhance the reversal of epidermal thickening and accelerate normalization of differentiation. Topical or injected IGF-I receptor antisense as adjunctive treatment will increase apoptosis in the epidermal layer thereby enhancing the reduction in acanthosis observed in UV treatments.

(iii) Survival of keratinocytes, ie. those which evade apoptosis is likely to occur when cells have damaged DNA. Such mutations may be in the tumor suppressor region. Consequently, the use of antisense therapy will result in less frequent selection of mutated keratinocytes and therefore reduced incidence of basal cell carcinomas and squamous.

According to this embodiment, there is provided a method for ameliorating the effects of a proliferative and/or inflammatory skin disorder such as psoriasis said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation with effective amounts of UV treatment and a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or inflammation.

The UV treatment and nucleic acid molecule or its chemical analogue may be administered in any order or may be done simultaneously. This method is particularly useful in treating psoriasis by combination of UV and antisense therapy. Preferably the antisense therapy is directed to the IGF-I receptor.

In a preferred embodiment, the present invention is directed to a method for ameliorating the effects of psoriasis or other medical disorder, said method comprising contacting proliferating skin or skin capable of proliferation or cells associated with said disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation or ameliorating the medical disorder.

The present invention extends to any mammal such as but not limited to humans, livestock animals (e.g. horses, sheep, cows, goats, pigs, donkeys), laboratory test animals (e.g. rabbits, mice, guinea pigs), companion animals (e.g. cats, dogs) and captive wild animals. However, the instant invention is particularly directed to proliferative and/or inflammatory skin disorders such as psoriasis in humans as well as medical disorders contemplated above.

The aspects of the subject invention instantly contemplated are particularly directed to the topical application of one or more suitable nucleic molecules capable of inhibiting, reducing or otherwise interfering with IGF-mediated cell proliferation and/or inflammation. More particularly, the nucleic acid molecule targets IGF-I interaction with its receptor. Conveniently, therefore, the nucleic acid molecule is an antagonist of IGF-I interaction with its receptor. Most conveniently, the nucleic acid molecule antagonist is an antisense molecule to the IGF-I receptor, to IGF-I itself or to a molecule capable of facilitating IGF-I interaction with its receptor such as but not limited to an IGFBP.

Insofar as the invention relates to IGFBPs, the preferred molecules are IGFBP-2, -3, -4, -5 and -6. The most preferred molecules are IGFBP-2 and IGFBP-3.

The nucleotide sequences of IGFBP-2 and IGFBP-3 are set forth in Figures 1 (<400>1) and 2 (<400>2), respectively. According to a particularly preferred aspect of the present invention, there is provided a nucleic acid molecule comprising at least about ten nucleotides capable of hybridising to, forming a heteroduplex or otherwise interacting with an mRNA molecule directed from a gene corresponding to a genomic form of <400>1 and/or <400>2 and which thereby reduces or inhibits translation of said mRNA molecule. Preferably, the nucleic acid molecule is at least about 15 nucleotides in length and more preferably at least about 20-25 nucleotides in length. However, the instant invention extends to any length nucleic acid molecule including a molecule of 100-200 nucleotides in length to correspond to the full length of or near full length of the subject genes.

The nucleotide sequence of the antisense molecules may correspond exactly to a region or portion of <400>1 or <400>2 or may differ by one or more nucleotide substitutions, deletions and/or additions. It is a requirement, however, that the nucleic acid molecule interact with an mRNA molecule to thereby reduce its translation into active protein.

Examples of potential antisense molecules for IGFBP-2 and IGFBP-3 are those capable of interacting with sequences selected from the lists in Examples 6 and 7, respectively.

The nucleic acid molecules in the form of an antisense molecule may be linear or covalently closed circular and single stranded or partially double stranded. A double stranded molecule may form a triplex with target mRNA or a target gene. The molecule may also be protected from, for example, nucleases, by any number of means such as using a nonionic backbone or a phosphorothioate linkage. A convenient nonionic backbone contemplated herein is ethylphosphotriester linkage or a 2′-O-methylribosyl derivative. A particularly useful modification modifies the DNA backbone by introducing phosphorothioate internucleotide linkages. Alternatively or in addition to the pyrimidine bases are modified by inclusion of a C-5 propyne substitution which modification is proposed to enhance duplex stability [23]. The present invention extends to any chemical modification to the bases and/or RNA or DNA backbone. Reference to a "chemical analogue" of a nucleic acid molecule includes reference to a modified base, nucleotide, nucleoside or phosphate backbone.

Examples of suitable oligonucleotide analogues are conveniently described in Ts'O *et al* [7]. Further suitable examples of oligonucleotide analogues and chemical modifications are described in references 25 to 31.

Alternatively, the antisense molecules of the present invention may target the IGF-I gene itself or its receptor or a multivalent antisense molecule may be constructed or separate molecules administered which target at least two or an IGFBP, IGF-I and/or IGF-I-receptor. Examples of suitable antisense molecules capable of targetting the IGF-I receptor are those capable of

interacting with sequences selected from the list in Example 8. One particularly useful antisense molecule is 5'- ATCTCTCCGCTTCCTTTC -3' (<400>10).

Other particularly useful antisense molecules are:

#27 UCCGGAGCCAGACUU

#64 CACAGUUGCUGCAAG

#78 UCUCCGCUUCCUUUC

#28 AGCCCCCACAGCGAG

#32 GCCUUGGAGAUGAGC

#40 UAACAGAGGUCAGCA

#42 GGAUCAGGGACCAGU

#46 CGGCAAGCUACACAG

#50 GGCAGGCAGGCACAC

Particularly useful molecules are selected from #27, #64 and #78. In a preferred embodiment these molecules comprise a C-5 propynyl dU, dC phosphorothioate modification.

A particularly preferred embodiment of the present invention contemplates a method of ameliorating the effects of psoriasis or other medical disorder, said method comprising contacting proliferating skin or skin capable of proliferation or cells associated with said medical disorder with an effective amount of one or more nucleic acid molecules or chemical analogues thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation or ameliorating the medical disorder wherein said one or more molecules comprises a polynucleotide capable of interacting with mRNA directed from an IGF-I gene, an IGF-I receptor gene or a gene encoding an IGFBP such as IGFBP-2 and/or IGFBP-3.

Preferably, the nucleic acid molecule are antisense molecules. Particularly useful antisense molecules are:

#27 UCCGGAGCCAGACUU

#64 CACAGUUGCUGCAAG

#78 UCUCCGCUUCCUUUC

#28 AGCCCCCACAGCGAG

#32 GCCUUGGAGAUGAGC

#40 UAACAGAGGUCAGCA

#42 GGAUCAGGGACCAGU

#46 CGGCAAGCUACACAG

#50 GGCAGGCAGGCACAC

Even more particularly useful molecules are selected from #27, #64 and #78.

In accordance with one aspect of the present invention the nucleic acid molecule is topically applied in aqueous solution or in conjunction with a cream, ointment, oil or other suitable carrier and/or diluent. A single application may be sufficient depending on the severity or exigencies of the condition although more commonly, multiple applications are required ranging from hourly, multi-hourly, daily, multi-daily, weekly or monthly, or in some other suitable time interval. The treatment might comprise solely the application of the nucleic acid molecule or this may be applied in conjunction with other treatments for the skin proliferation and/or inflammatory disorder being treated or for other associated conditions including microbial infection, bleeding and the formation of a variety of rashes.

As an alternative to or in conjunction with antisense therapy, the subject invention extends to the nucleic acid molecule as, or incorporating, a ribozyme including a minizyme to, for example, IGF-I, its receptor or to molecules such as IGFBPs and in particular IGFBP-2 and -3. Ribozymes are synthetic nucleic acid molecules which possess highly specific endoribonuclease activity. In particular, they comprise a hybridising region which is complementary in nucleotide sequence to at least part of a target RNA. Ribozymes are well described by Haseloff and Gerlach [8] and in International Patent Application No. WO 89/05852. The present invention extends to ribozymes which target mRNA specified by genes encoding IGF-I, its receptor or one or more IGFBPs such as IGFBP-2 and/or IGFBP-3.

According to this embodiment, there is provided in a particularly preferred aspect a ribozyme comprising a hybridising region and a catalytic region wherein the hybridising region is capable of hybridising to at least part of a target mRNA sequence transcribed from a genomic gene corresponding to (<400>1) or (<400>2) wherein said catalytic domain is capable of cleaving said target mRNA sequence to reduce or inhibit IGF-I mediated cell proliferation and/or inflammation and/or other medical disorders.

Yet another aspect of the present invention contemplates co-suppression to reduce expression or to inhibit translation of an endogenous gene encoding, for example, IGF-I, its receptor, or IGFBPs such as IGFBP-2 and/or -3. In co-suppression, a second copy of an endogenous gene or a substantially similar copy or analogue of an endogenous gene is introduced into a cell following topical administration. As with antisense molecules, nucleic acid molecules defining a ribozyme or nucleic acid molecules useful in co-suppression may first be protected such as by using a nonionic backbone.

The efficacy of the nucleic acid molecules of the present invention can be conveniently tested and screened using an *in vitro* system comprising a basal keratinocyte cell line. A particularly useful system comprises the HaCaT cell line described by Boukamp *et al* [9]. In one assay, IGF-I is added to an oligonucleotide treated HaCaT cell line. Alternatively, growth of oligonucleotide treated HaCaT cells is observed on a feeder layer of irradiated 3T3 fibroblasts. Using such *in vitro* assays, it is observed that antisense oligonucleotides to IGFBP-3, for example, inhibit production of IGFBP-3 by HaCaT cells. Other suitable animal models include the nude mouse/human skin graft model (15; 16) and the "flaky skin" mouse model (17; 18). In the nude mouse model, microdermatome biopsies of psoriasis lesions are taken under local anaesthetic from volunteers then transplanted to congenital athymic (nude) mice. These transplanted human skin grafts maintain the characteristic hyperproliferating epidermis for 6-8 weeks. They are an established model for testing the efficacy of topically applied therapies for psoriasis. In the "flaky skin" mouse model, the fsn/fsn mutation produces mice with skin resembling human psoriasis. This mouse, or another mutant mouse with a similar phenotype is a further *in vivo* model to test the efficacy of topically applied therapies for psoriasis.

Another aspect of the present invention contemplates a pharmaceutical composition for topical administration which comprises a nucleic acid molecule capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation such as psoriasis and one or more pharmaceutically acceptable carriers and/or diluents. Preferably, the nucleic acid molecule is an antisense molecule to IGF-I, the IGF-I receptor or an IGFBP such as IGFBP-2 and/or IGFBP-3 or comprises a ribozyme to one or more of these targets or is a molecule suitable for co-suppression of one or more of these targets. The composition may comprise a single species of a nucleic acid molecule capable of targeting one of IGF-I, its receptor or an IGFBP, such as IGFBP-2 or IGFBP-3 or may be a multi-valent molecule capable of targeting two or more of IGF-I, its receptor or an IGFBP, such as IGFBP-2 and/or IGFBP-3.

The nucleic acid molecules may be administered in dispersions prepared in creams, ointments, oil or other suitable carrier and/or diluent such as glycerol, liquid polyethylene glycols and/or mixtures thereof. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for topical use include sterile aqueous solutions (where water soluble) or dispersions and powders for the extemporaneous preparation of topical solutions or dispersions. In all cases, the form is preferably sterile although this is not an absolute requirement and is stable under the conditions of manufacture and storage. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of superfactants. The prevention of the action of microorganism can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride.

Topical solutions are prepared by incorporating the nucleic acid molecule compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by where necessary filter sterilization.

The active agent may alternatively be administered by intravenous, subcutaneous, nasal drip, suppository, implant means amongst other suitable routes of administration including intraperitoneal, intramuscular, absorption through epithelial or mucocutaneous linings for example via nasal, oral, vaginal, rectal or gastrointestinal administration. Reference may conveniently be made to reference 24.

As used herein "pharmaceutically acceptable carriers and/or diluents" include any and all solvents, dispersion media, aqueous solutions, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, use thereof in the pharmaceutical compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. Conveniently, the nucleic acid molecules of the present invention are stored in freeze-dried form and are reconstituted prior to use.

Yet another aspect of the present invention contemplates the use of a nucleic acid molecule in the manufacture of a medicament for the treatment of proliferative and/or inflammatory skin disorders or other medical disorders mediated by a growth factor. The proliferative and/or inflammatory skin disorder is generally psoriasis or other medical disorders as described above and the nucleic acid molecule targets IGF-I, the IGF-I receptor and/or an IGFBP such as IGFBP-2 and/or IGFBP-3.

Still a further aspect of the present invention contemplates an agent comprising a nucleic acid molecule as hereinbefore defined useful in the treatment of proliferative and/or inflammatory skin disorders, such as psoriasis or other medical disorder..

The present invention further contemplates the use of the genetic molecules and in particular the antisense molecules to inhibit the anti-apoptotic activity of IGF-I receptor. Such a use is appropriate for the treatment of certain cancers and as adjunct therapy for epidermal hyperplasia such as in combination with UV treatment.

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The present invention is further described by the following non-limiting Examples.

## EXAMPLE 1

The differentiated human keratinocyte cell line, HaCaT [9] was used in the *in vitro* assay. Cells at passage numbers 33 to 36 were maintained as monolayer cultures in 5% v/v $CO_2$ at 37°C in Keratinocyte-SFM (Gibco) containing EGF and bovine pituitary extract as supplied. Media containing foetal calf serum were avoided because of the high content of IGF-I binding proteins in serum.

Feeder layer plates of lethally irradiated 3T3 fibroblasts were prepared exactly as described by Rheinwald and Green [10].

## EXAMPLE 2

Cells were grown to 4 days post confluence in $2cm^2$ wells with daily medium changes of Keratinocyte-SFM, then the medium was changed to DMEM (Cytosystems, Australia), with the following additions: 25mM Hepes, 0.19% w/v, sodium bicarbonate, 0.03% w/v glutamine (Sigma Chemical Co, USA), 50IU/ml penicillin and 50µg/ml streptomycin (Flow Laboratories). After 24 hours, IGF-I or tIGF-I was added to triplicate wells, at the concentrations indicated, in 0.5ml fresh DMEM containing 0.02% v/v bovine serum albumin (Sigma molecular biology grade) and incubated for a further 21 hours. [$^3$H]-Thymidine (0.1µCi/well) was then added and the cells incubated for a further 3 hours. The medium was then aspirated and the cells washed once with ice-cold PBS and twice with ice-cold 10% v/v TCA. The TCA-precipitated monolayers were then solubilized with 0.25M NaOH (200µl/well), transferred to scintillation vials and radioactivity determined by liquid scintillation counting (Pharmacia Wallac 1410 liquid scintillation counter).

## EXAMPLE 3

HaCaT conditioned medium (250µl) was concentrated by adding 750µl cold ethanol, incubating at -20°C for 2 hours and centrifuging at 16,000g for 20 min at 4°C. The resulting pellet was air dried, resuspended thoroughly in non-reducing Laemmli sample buffer, heated to 90°C for 5 minutes and separated on 12% w/v SDS-PAGE according to the method of Laemmli (1970). Separated proteins were electrophoretically transferred to nitrocellulose membrane (0.45mm, Schleicher and Schuell, Dassel, Germany) in a buffer containing 25mM Tris, 192mM glycine

and 20% v/v methanol. IGFBPs were then visualised by the procedure of Hossenlopp *et al* [11], using [$^{125}$I]-IGF-I, followed by autoradiography. Autoradiographs were scanned in a BioRad Model GS-670 Imaging Densitometer and band densities were determined using the Molecular Analyst program.

**EXAMPLE 4**

Phosphorothioate oligodeoxynucleotides were synthesised by Bresatec, Adelaide, South Australia, Australia. The following antisense sequences were used: BP3AS2, 5'- GCG CCC GCT GCA TGA CGC CTG CAA C -3' (<400>4), a 25mer complementary to the start codon region of the human IGFBP-3 mRNA; BP3AS3, 5'- CGG GCG GCT CAC CTG GAG CTG GCG -3' (<400>5), a 24mer complementary to the exon 1/intron 1 splice site; BP3AS4, 5'- AGG CGG CTG ACG GCA CTA -3'(<400>6), an 18mer complementary to a region of the coding sequence lacking RNA secondary structure and oligonucleotide-dimer formation (using the computer software "OLIGO for PC"). Since BP3AS4 was found to be ineffective at inhibiting IGFBP-3 synthesis, it was used as a control. The following additional control oligonucleotide sequences were used: BP3S, 5'- CAG GCG TCA TGC AGC GGG C -3' (<400>7), an 18mer sense control sequence equivalent to the start codon region; BP3AS2NS, 5'- CGG AGA TGC CGC ATG CCA GCG CAG G -3' (<400>8), a 25mer randomised sequence with the same GC content as BP3AS2; BP3AS4NS, 5'- GAC AGC GTC GGA GCG ATC -3' (<400>9), an 18mer randomised sequence with the same GC content as BP3AS4NS. Design of the oligonucleotides was based on the human IGFBP-3 cDNA sequence of Spratt *et al* [12].

Cells were grown to one day post confluence in 2cm$^2$ wells with daily medium changes of 0.5ml Keratinocyte-SFM, then subjected to daily medium changes of Keratinocyte-SFM for a further 4 days. Daily additions of 0.5ml fresh Keratinocyte-SFM were then continued for a further 7 days, except that at the time of medium addition, 5µl oligonucleotide in PBS was added to give the final concentrations indicated, then the wells were shaken to mix the oligonucleotide. After the final addition, cells were incubated for 24 hours and the medium collected for assay of IGFBPs. Cells were then counted after trypsinisation in a Coulter Industrial D Counter, Coulter Bedfordshire, UK. Cell numbers after oligonucleotide treatment differed by less than 10%.

## EXAMPLE 5

HaCaT cells secrete mainly IGFBP-3 (>95%), with the only other IGFBP detectable in HaCaT conditioned medium being IGFBP-4 (<5%). The effect on IGFBP-3 and IGFBP-4 synthesis of antisense oligonucleotides at two concentrations, 5μM and 0.5μM, was tested. Two oligonucleotides were used, BP3AS2 and BP3AS3, directed against the start site and the intron 1/exon 1 splice site, respectively of the IGFBP-3 mRNA. As a control, a sense oligonucleotide corresponding to the start site was used. As shown in Figures 4A and 4B, all oligonucleotides at 5μM caused a significant reduction of IGFBP-3 synthesis compared with untreated cells, however, the two antisense oligonucleotides inhibited IGFBP-3 synthesis of approximately 50% compared to the sense control (Figure 4B). The antisense oligonucleotide directed to the start codon appeared to be more effective of the two, the difference being more apparent at the lower concentration of 0.5μM. The cells of IGFBP-4 secreted by the HaCaT cells make photographic reproduction of the bands on Western ligand blots difficult, however densitometry measurements provide adequate relative quantitation. This resulted in the significant observation that IGFBP-4 levels were unaffected by oligonucleotide addition to the cells, suggesting that the observed inhibitory effects on IGFBP-3 are specific.

To further investigate the inhibitory effects of the more effective of the two antisense oligonucleotides, BP3AS2, inhibition by this oligonucleotide at 0.5μM was compared with a number of control oligonucleotides, including one antisense oligonucleotide to IGFBP-3 that had proved to be ineffective at 0.5μM. As shown in Figures 5A and 5B, BP3AS2 was again inhibitory, resulting in levels of IGFBP-3 of approximately 50% of the most non-specifically inhibitory control oligonucleotide, the randomised equivalent of BP3AS2. The other control oligonucleotides caused no reduction in IGFBP-3 levels at 0.5μM, compared to untreated cells. Of possible significance is the fact that this control oligonucleotide, BP3AS2NS, like BP3AS2 itself, has the highest potential $T_m$ of the three control oligonucleotides used in this experiment, enhancing the probability of non-specific base pairing with non-target mRNAs. However, the lack of inhibition of IGFBP-4 secretion by BP3AS2 suggests that this oligonucleotide is selective even compared with the most closely related protein likely to be present in this cell line.

## EXAMPLE 6

Antisense oligonucleotides to IGFBP2 may be selected from molecules capable of interacting with one or more of the following sense oligonucleotides:

| | | |
|---|---|---|
| ATTCGGGGCGAGGGA | CGCAGGGCCGTGCAC | CCGCGCCGCGCTGCC |
| TTCGGGGCGAGGGAG | GCAGGGCCGTGCACC | CGCGCCGCGCTGCCG |
| TCGGGGCGAGGGAGG | CAGGGCCGTGCACCT | GCGCCGCGCTGCCGA |
| CGGGGCGAGGGAGGA | AGGGCCGTGCACCTG | CGCCGCGCTGCCGAC |
| GGGGCGAGGGAGGAG | GGGCCGTGCACCTGC | GCCGCGCTGCCGACC |
| GGGCGAGGGAGGAGG | GGCCGTGCACCTGCC | CCGCGCTGCCGACCG |
| GGCGAGGGAGGAGGA | GCCGTGCACCTGCCC | CGCGCTGCCGACCGC |
| GCGAGGGAGGAGGAA | CCGTGCACCTGCCCG | GCGCTGCCGACCGCC |
| CGAGGGAGGAGGAAG | CGTGCACCTGCCCGC | CGCTGCCGACCGCCA |
| GAGGGAGGAGGAAGA | GTGCACCTGCCCGCC | GCTGCCGACCGCCAG |
| AGGGAGGAGGAAGAA | TGCACCTGCCCGCCC | CTGCCGACCGCCAGC |
| GGGAGGAGGAAGAAG | GCACCTGCCCGCCCG | TGCCGACCGCCAGCA |
| GGAGGAGGAAGAAGC | CACCTGCCCGCCCGC | GCCGACCGCCAGCAT |
| GAGGAGGAAGAAGCG | ACCTGCCCGCCCGCC | CCGACCGCCAGCATG |
| AGGAGGAAGAAGCGG | CCTGCCCGCCCGCCC | CGACCGCCAGCATGC |
| GGAGGAAGAAGCGGA | CTGCCCGCCCGCCCG | GACCGCCAGCATGCT |
| GAGGAAGAAGCGGAG | TGCCCGCCCGCCCGC | ACCGCCAGCATGCTG |
| AGGAAGAAGCGGAGG | GCCCGCCCGCCCGCT | CCGCCAGCATGCTGC |
| GGAAGAAGCGGAGGA | CCCGCCCGCCCGCTC | CGCCAGCATGCTGCC |
| GAAGAAGCGGAGGAG | CCGCCCGCCCGCTCG | GCCAGCATGCTGCCG |
| AAGAAGCGGAGGAGG | CGCCCGCCCGCTCGC | CCAGCATGCTGCCGA |
| AGAAGCGGAGGAGGC | GCCCGCCCGCTCGCT | CAGCATGCTGCCGAG |
| GAAGCGGAGGAGGCG | CCCGCCCGCTCGCTC | AGCATGCTGCCGAGA |
| AAGCGGAGGAGGCGG | CCGCCCGCTCGCTCG | GCATGCTGCCGAGAG |
| AGCGGAGGAGGCGGC | CGCCCGCTCGCTCGC | CATGCTGCCGAGAGT |
| GCGGAGGAGGCGGCT | GCCCGCTCGCTCGCT | ATGCTGCCGAGAGTG |
| CGGAGGAGGCGGCTC | CCCGCTCGCTCGCTC | TGCTGCCGAGAGTGG |
| GGAGGAGGCGGCTCC | CCGCTCGCTCGCTCG | GCTGCCGAGAGTGGG |
| GAGGAGGCGGCTCCC | CGCTCGCTCGCTCGC | CTGCCGAGAGTGGGC |
| AGGAGGCGGCTCCCG | GCTCGCTCGCTCGCC | TGCCGAGAGTGGGCT |
| GGAGGCGGCTCCCGC | CTCGCTCGCTCGCCC | GCCGAGAGTGGGCTG |
| GAGGCGGCTCCCGCT | TCGCTCGCTCGCCCG | CCGAGAGTGGGCTGC |
| AGGCGGCTCCCGCTC | CGCTCGCTCGCCCGC | CGAGAGTGGGCTGCC |
| GGCGGCTCCCGCTCG | GCTCGCTCGCCCGCC | GAGAGTGGGCTGCCC |
| GCGGCTCCCGCTCGC | CTCGCTCGCCCGCCG | AGAGTGGGCTGCCCC |
| CGGCTCCCGCTCGCA | TCGCTCGCCCGCCGC | GAGTGGGCTGCCCCG |
| GGCTCCCGCTCGCAG | CGCTCGCCCGCCGCG | AGTGGGCTGCCCCGC |
| GCTCCCGCTCGCAGG | GCTCGCCCGCCGCGC | GTGGGCTGCCCCGCG |
| CTCCCGCTCGCAGGG | CTCGCCCGCCGCGCC | TGGGCTGCCCCGCGC |
| TCCCGCTCGCAGGGC | TCGCCCGCCGCGCCG | GGGCTGCCCCGCGCT |
| CCCGCTCGCAGGGCC | CGCCCGCCGCGCCGC | GGCTGCCCCGCGCTG |
| CCGCTCGCAGGGCCG | GCCCGCCGCGCCGCG | GCTGCCCCGCGCTGC |
| CGCTCGCAGGGCCGT | CCCGCCGCGCCGCGC | CTGCCCCGCGCTGCC |
| GCTCGCAGGGCCGTG | CCGCCGCGCCGCGCT | TGCCCCGCGCTGCCG |
| CTCGCAGGGCCGTGC | CGCCGCGCCGCGCTG | GCCCCGCGCTGCCGC |
| TCGCAGGGCCGTGCA | GCCGCGCCGCGCTGC | CCCCGCGCTGCCGCT |

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|---|---|---|
| CCCGCGCTGCCGCTG | CTGCTGCTACTGGGC | CTGTTCCGCTGCCCG |
| CCGCGCTGCCGCTGC | TGCTGCTACTGGGCG | TGTTCCGCTGCCCGC |
| CGCGCTGCCGCTGCC | GCTGCTACTGGGCGC | GTTCCGCTGCCCGCC |
| GCGCTGCCGCTGCCG | CTGCTACTGGGCGCG | TTCCGCTGCCCGCCC |
| CGCTGCCGCTGCCGC | TGCTACTGGGCGCGA | TCCGCTGCCCGCCCT |
| GCTGCCGCTGCCGCC | GCTACTGGGCGCGAG | CCGCTGCCCGCCCTG |
| CTGCCGCTGCCGCCG | CTACTGGGCGCGAGT | CGCTGCCCGCCCTGC |
| TGCCGCTGCCGCCGC | TACTGGGCGCGAGTG | GCTGCCCGCCCTGCA |
| GCCGCTGCCGCCGCC | ACTGGGCGCGAGTGG | CTGCCCGCCCTGCAC |
| CCGCTGCCGCCGCCG | CTGGGCGCGAGTGGC | TGCCCGCCCTGCACA |
| CGCTGCCGCCGCCGC | TGGGCGCGAGTGGCG | GCCCGCCCTGCACAC |
| GCTGCCGCCGCCGCC | GGGCGCGAGTGGCGG | CCCGCCCTGCACACC |
| CTGCCGCCGCCGCCG | GGCGCGAGTGGCGGC | CCGCCCTGCACACCC |
| TGCCGCCGCCGCCGC | GCGCGAGTGGCGGCG | CGCCCTGCACACCCG |
| GCCGCCGCCGCCGCT | CGCGAGTGGCGGCGG | GCCCTGCACACCCGA |
| CCGCCGCCGCCGCTG | GCGAGTGGCGGCGGC | CCCTGCACACCCGAG |
| CGCCGCCGCCGCTGC | CGAGTGGCGGCGGCG | CCTGCACACCCGAGC |
| GCCGCCGCCGCTGCT | GAGTGGCGGCGGCGG | CTGCACACCCGAGCG |
| CCGCCGCCGCTGCTG | AGTGGCGGCGGCGGC | TGCACACCCGAGCGC |
| CGCCGCCGCTGCTGC | GTGGCGGCGGCGGCG | GCACACCCGAGCGCC |
| GCCGCCGCTGCTGCC | TGGCGGCGGCGGCGG | CACACCCGAGCGCCT |
| CCGCCGCTGCTGCCG | GGCGGCGGCGGCGGG | ACACCCGAGCGCCTG |
| CGCCGCTGCTGCCGC | GCGGCGGCGGCGGGG | CACCCGAGCGCCTGG |
| GCCGCTGCTGCCGCT | CGGCGGCGGCGGGGC | ACCCGAGCGCCTGGC |
| CCGCTGCTGCCGCTG | GGCGGCGGCGGGGCG | CCCGAGCGCCTGGCC |
| CGCTGCTGCCGCTGC | GCGGCGGCGGGGCGC | CCGAGCGCCTGGCCG |
| GCTGCTGCCGCTGCT | CGGCGGCGGGGCGCG | CGAGCGCCTGGCCGC |
| CTGCTGCCGCTGCTG | GGCGGCGGGGCGCGC | GAGCGCCTGGCCGCC |
| TGCTGCCGCTGCTGC | GCGGCGGGGCGCGCG | AGCGCCTGGCCGCCT |
| GCTGCCGCTGCTGCC | CGGCGGGGCGCGCGC | GCGCCTGGCCGCCTG |
| CTGCCGCTGCTGCCG | GGCGGGGCGCGCGCG | CGCCTGGCCGCCTGC |
| TGCCGCTGCTGCCGC | GCGGGGCGCGCGCGG | GCCTGGCCGCCTGCG |
| GCCGCTGCTGCCGCT | CGGGGCGCGCGCGGA | CCTGGCCGCCTGCGG |
| CCGCTGCTGCCGCTG | GGGGCGCGCGCGGAG | CTGGCCGCCTGCGGG |
| CGCTGCTGCCGCTGC | GGGCGCGCGCGGAGG | TGGCCGCCTGCGGGC |
| GCTGCTGCCGCTGCT | GGCGCGCGCGGAGGT | GGCCGCCTGCGGGCC |
| CTGCTGCCGCTGCTG | GCGCGCGCGGAGGTG | GCCGCCTGCGGGCCC |
| TGCTGCCGCTGCTGC | CGCGCGCGGAGGTGC | CCGCCTGCGGGCCCC |
| GCTGCCGCTGCTGCT | GCGCGCGGAGGTGCT | CGCCTGCGGGCCCCC |
| CTGCCGCTGCTGCTG | CGCGCGGAGGTGCTG | GCCTGCGGGCCCCCG |
| TGCCGCTGCTGCTGC | GCGCGGAGGTGCTGT | CCTGCGGGCCCCCGC |
| GCCGCTGCTGCTGCT | CGCGGAGGTGCTGTT | CTGCGGGCCCCCGCC |
| CCGCTGCTGCTGCTG | GCGGAGGTGCTGTTC | TGCGGGCCCCCGCCG |
| CGCTGCTGCTGCTGC | CGGAGGTGCTGTTCC | GCGGGCCCCCGCCGG |
| GCTGCTGCTGCTGCT | GGAGGTGCTGTTCCG | CGGGCCCCCGCCGGT |
| CTGCTGCTGCTGCTA | GAGGTGCTGTTCCGC | GGGCCCCCGCCGGTT |
| TGCTGCTGCTGCTAC | AGGTGCTGTTCCGCT | GGCCCCCGCCGGTTG |
| GCTGCTGCTGCTACT | GGTGCTGTTCCGCTG | GCCCCCGCCGGTTGC |
| CTGCTGCTGCTACTG | GTGCTGTTCCGCTGC | CCCCCGCCGGTTGCG |
| TGCTGCTGCTACTGG | TGCTGTTCCGCTGCC | CCCCGCCGGTTGCGC |
| GCTGCTGCTACTGGG | GCTGTTCCGCTGCCC | CCCGCCGGTTGCGCC |

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|---|---|---|---|
| | CCGCCGGTTGCGCCG | ATGCCATGCGCGGAG | TGCGCCCGGCTGGAG |
| | CGCCGGTTGCGCCGC | TGCCATGCGCGGAGC | GCGCCCGGCTGGAGG |
| | GCCGGTTGCGCCGCC | GCCATGCGCGGAGCT | CGCCCGGCTGGAGGG |
| | CCGGTTGCGCCGCCC | CCATGCGCGGAGCTC | GCCCGGCTGGAGGGC |
| 5 | CGGTTGCGCCGCCCG | CATGCGCGGAGCTCG | CCCGGCTGGAGGGCG |
| | GGTTGCGCCGCCCGC | ATGCGCGGAGCTCGT | CCGGCTGGAGGGCGA |
| | GTTGCGCCGCCCGCC | TGCGCGGAGCTCGTC | CGGCTGGAGGGCGAG |
| | TTGCGCCGCCCGCCG | GCGCGGAGCTCGTCC | GGCTGGAGGGCGAGG |
| | TGCGCCGCCCGCCGC | CGCGGAGCTCGTCCG | GCTGGAGGGCGAGGC |
| 10 | GCGCCGCCCGCCGCG | GCGGAGCTCGTCCGG | CTGGAGGGCGAGGCG |
| | CGCCGCCCGCCGCGG | CGGAGCTCGTCCGGG | TGGAGGGCGAGGCGT |
| | GCCGCCCGCCGCGGT | GGAGCTCGTCCGGGA | GGAGGGCGAGGCGTG |
| | CCGCCCGCCGCGGTG | GAGCTCGTCCGGGAG | GAGGGCGAGGCGTGC |
| | CGCCCGCCGCGGTGG | AGCTCGTCCGGGAGC | AGGGCGAGGCGTGCG |
| 15 | GCCCGCCGCGGTGGC | GCTCGTCCGGGAGCC | GGGCGAGGCGTGCGG |
| | CCCGCCGCGGTGGCC | CTCGTCCGGGAGCCG | GGCGAGGCGTGCGGC |
| | CCGCCGCGGTGGCCG | TCGTCCGGGAGCCGG | GCGAGGCGTGCGGCG |
| | CGCCGCGGTGGCCGC | CGTCCGGGAGCCGGG | CGAGGCGTGCGGCGT |
| | GCCGCGGTGGCCGCA | GTCCGGGAGCCGGGC | GAGGCGTGCGGCGTC |
| 20 | CCGCGGTGGCCGCAG | TCCGGGAGCCGGGCT | AGGCGTGCGGCGTCT |
| | CGCGGTGGCCGCAGT | CCGGGAGCCGGGCTG | GGCGTGCGGCGTCTA |
| | GCGGTGGCCGCAGTG | CGGGAGCCGGGCTGC | GCGTGCGGCGTCTAC |
| | CGGTGGCCGCAGTGG | GGGAGCCGGGCTGCG | CGTGCGGCGTCTACA |
| | GGTGGCCGCAGTGGC | GGAGCCGGGCTGCGG | GTGCGGCGTCTACAC |
| 25 | GTGGCCGCAGTGGCC | GAGCCGGGCTGCGGC | TGCGGCGTCTACACC |
| | TGGCCGCAGTGGCCG | AGCCGGGCTGCGGCT | GCGGCGTCTACACCC |
| | GGCCGCAGTGGCCGG | GCCGGGCTGCGGCTG | CGGCGTCTACACCCC |
| | GCCGCAGTGGCCGGA | CCGGGCTGCGGCTGC | GGCGTCTACACCCCG |
| | CCGCAGTGGCCGGAG | CGGGCTGCGGCTGCT | GCGTCTACACCCCGC |
| 30 | CGCAGTGGCCGGAGG | GGGCTGCGGCTGCTG | CGTCTACACCCCGCG |
| | GCAGTGGCCGGAGGC | GGCTGCGGCTGCTGC | GTCTACACCCCGCGC |
| | CAGTGGCCGGAGGCG | GCTGCGGCTGCTGCT | TCTACACCCCGCGCT |
| | AGTGGCCGGAGGCGC | CTGCGGCTGCTGCTC | CTACACCCCGCGCTG |
| | GTGGCCGGAGGCGCC | TGCGGCTGCTGCTCG | TACACCCCGCGCTGC |
| 35 | TGGCCGGAGGCGCCC | GCGGCTGCTGCTCGG | ACACCCCGCGCTGCG |
| | GGCCGGAGGCGCCCG | CGGCTGCTGCTCGGT | CACCCCGCGCTGCGG |
| | GCCGGAGGCGCCCGC | GGCTGCTGCTCGGTG | ACCCCGCGCTGCGGC |
| | CCGGAGGCGCCCGCA | GCTGCTGCTCGGTGT | CCCCGCGCTGCGGCC |
| | CGGAGGCGCCCGCAT | CTGCTGCTCGGTGTG | CCCGCGCTGCGGCCA |
| 40 | GGAGGCGCCCGCATG | TGCTGCTCGGTGTGC | CCGCGCTGCGGCCAG |
| | GAGGCGCCCGCATGC | GCTGCTCGGTGTGCG | CGCGCTGCGGCCAGG |
| | AGGCGCCCGCATGCC | CTGCTCGGTGTGCGC | GCGCTGCGGCCAGGG |
| | GGCGCCCGCATGCCA | TGCTCGGTGTGCGCC | CGCTGCGGCCAGGGG |
| | GCGCCCGCATGCCAT | GCTCGGTGTGCGCCC | GCTGCGGCCAGGGGC |
| 45 | CGCCCGCATGCCATG | CTCGGTGTGCGCCCG | CTGCGGCCAGGGGCT |
| | GCCCGCATGCCATGC | TCGGTGTGCGCCCGG | TGCGGCCAGGGGCTG |
| | CCCGCATGCCATGCG | CGGTGTGCGCCCGGC | GCGGCCAGGGGCTGC |
| | CCGCATGCCATGCGC | GGTGTGCGCCCGGCT | CGGCCAGGGGCTGCG |
| | CGCATGCCATGCGCG | GTGTGCGCCCGGCTG | GGCCAGGGGCTGCGC |
| 50 | GCATGCCATGCGCGG | TGTGCGCCCGGCTGG | GCCAGGGGCTGCGCT |
| | CATGCCATGCGCGGA | GTGCGCCCGGCTGGA | CCAGGGGCTGCGCTG |

| | | | |
|---|---|---|---|
| | CAGGGGCTGCGCTGC | CTGGTCATGGGCGAG | GCCAGCCCGGAGCAG |
| | AGGGGCTGCGCTGCT | TGGTCATGGGCGAGG | CCAGCCCGGAGCAGG |
| | GGGGCTGCGCTGCTA | GGTCATGGGCGAGGG | CAGCCCGGAGCAGGT |
| | GGGCTGCGCTGCTAT | GTCATGGGCGAGGGC | AGCCCGGAGCAGGTT |
| 5 | GGCTGCGCTGCTATC | TCATGGGCGAGGGCA | GCCCGGAGCAGGTTG |
| | GCTGCGCTGCTATCC | CATGGGCGAGGGCAC | CCCGGAGCAGGTTGC |
| | CTGCGCTGCTATCCC | ATGGGCGAGGGCACT | CCGGAGCAGGTTGCA |
| | TGCGCTGCTATCCCC | TGGGCGAGGGCACTT | CGGAGCAGGTTGCAG |
| | GCGCTGCTATCCCCA | GGGCGAGGGCACTTG | GGAGCAGGTTGCAGA |
| 10 | CGCTGCTATCCCCAC | GGCGAGGGCACTTGT | GAGCAGGTTGCAGAC |
| | GCTGCTATCCCCACC | GCGAGGGCACTTGTG | AGCAGGTTGCAGACA |
| | CTGCTATCCCCACCC | CGAGGGCACTTGTGA | GCAGGTTGCAGACAA |
| | TGCTATCCCCACCCG | GAGGGCACTTGTGAG | CAGGTTGCAGACAAT |
| | GCTATCCCCACCCGG | AGGGCACTTGTGAGA | AGGTTGCAGACAATG |
| 15 | CTATCCCCACCCGGG | GGGCACTTGTGAGAA | GGTTGCAGACAATGG |
| | TATCCCCACCCGGGC | GGCACTTGTGAGAAG | GTTGCAGACAATGGC |
| | ATCCCCACCCGGGCT | GCACTTGTGAGAAGC | TTGCAGACAATGGCG |
| | TCCCCACCCGGGCTC | CACTTGTGAGAAGCG | TGCAGACAATGGCGA |
| | CCCCACCCGGGCTCC | ACTTGTGAGAAGCGC | GCAGACAATGGCGAT |
| 20 | CCCACCCGGGCTCCG | CTTGTGAGAAGCGCC | CAGACAATGGCGATG |
| | CCACCCGGGCTCCGA | TTGTGAGAAGCGCCG | AGACAATGGCGATGA |
| | CACCCGGGCTCCGAG | TGTGAGAAGCGCCGG | GACAATGGCGATGAC |
| | ACCCGGGCTCCGAGC | GTGAGAAGCGCCGGG | ACAATGGCGATGACC |
| | CCCGGGCTCCGAGCT | TGAGAAGCGCCGGGA | CAATGGCGATGACCA |
| 25 | CCGGGCTCCGAGCTG | GAGAAGCGCCGGGAC | AATGGCGATGACCAC |
| | CGGGCTCCGAGCTGC | AGAAGCGCCGGGACG | ATGGCGATGACCACT |
| | GGGCTCCGAGCTGCC | GAAGCGCCGGGACGC | TGGCGATGACCACTC |
| | GGCTCCGAGCTGCCC | AAGCGCCGGGACGCC | GGCGATGACCACTCA |
| | GCTCCGAGCTGCCCC | AGCGCCGGGACGCCG | GCGATGACCACTCAG |
| 30 | CTCCGAGCTGCCCCT | GCGCCGGGACGCCGA | CGATGACCACTCAGA |
| | TCCGAGCTGCCCCTG | CGCCGGGACGCCGAG | GATGACCACTCAGAA |
| | CCGAGCTGCCCCTGC | GCCGGGACGCCGAGT | ATGACCACTCAGAAG |
| | CGAGCTGCCCCTGCA | CCGGGACGCCGAGTA | TGACCACTCAGAAGG |
| | GAGCTGCCCCTGCAG | CGGGACGCCGAGTAT | GACCACTCAGAAGGA |
| 35 | AGCTGCCCCTGCAGG | GGGACGCCGAGTATG | ACCACTCAGAAGGAG |
| | GCTGCCCCTGCAGGC | GGACGCCGAGTATGG | CCACTCAGAAGGAGG |
| | CTGCCCCTGCAGGCG | GACGCCGAGTATGGC | CACTCAGAAGGAGGC |
| | TGCCCCTGCAGGCGC | ACGCCGAGTATGGCG | ACTCAGAAGGAGGCC |
| | GCCCCTGCAGGCGCT | CGCCGAGTATGGCGC | CTCAGAAGGAGGCCT |
| 40 | CCCCTGCAGGCGCTG | GCCGAGTATGGCGCC | TCAGAAGGAGGCCTG |
| | CCCTGCAGGCGCTGG | CCGAGTATGGCGCCA | CAGAAGGAGGCCTGG |
| | CCTGCAGGCGCTGGT | CGAGTATGGCGCCAG | AGAAGGAGGCCTGGT |
| | CTGCAGGCGCTGGTC | GAGTATGGCGCCAGC | GAAGGAGGCCTGGTG |
| | TGCAGGCGCTGGTCA | AGTATGGCGCCAGCC | AAGGAGGCCTGGTGG |
| 45 | GCAGGCGCTGGTCAT | GTATGGCGCCAGCCC | AGGAGGCCTGGTGGA |
| | CAGGCGCTGGTCATG | TATGGCGCCAGCCCG | GGAGGCCTGGTGGAG |
| | AGGCGCTGGTCATGG | ATGGCGCCAGCCCGG | GAGGCCTGGTGGAGA |
| | GGCGCTGGTCATGGG | TGGCGCCAGCCCGGA | AGGCCTGGTGGAGAA |
| | GCGCTGGTCATGGGC | GGCGCCAGCCCGGAG | GGCCTGGTGGAGAAC |
| 50 | CGCTGGTCATGGGCG | GCGCCAGCCCGGAGC | GCCTGGTGGAGAACC |
| | GCTGGTCATGGGCGA | CGCCAGCCCGGAGCA | CCTGGTGGAGAACCA |

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|---|---|---|
| CTGGTGGAGAACCAC | AGTGCTGGCCGGAAG | CGGGAGAAGGTCACT |
| TGGTGGAGAACCACG | GTGCTGGCCGGAAGC | GGGAGAAGGTCACTG |
| GGTGGAGAACCACGT | TGCTGGCCGGAAGCC | GGAGAAGGTCACTGA |
| GTGGAGAACCACGTG | GCTGGCCGGAAGCCC | GAGAAGGTCACTGAG |
| TGGAGAACCACGTGG | CTGGCCGGAAGCCCC | AGAAGGTCACTGAGC |
| GGAGAACCACGTGGA | TGGCCGGAAGCCCCT | GAAGGTCACTGAGCA |
| GAGAACCACGTGGAC | GGCCGGAAGCCCCTC | AAGGTCACTGAGCAG |
| AGAACCACGTGGACA | GCCGGAAGCCCCTCA | AGGTCACTGAGCAGC |
| GAACCACGTGGACAG | CCGGAAGCCCCTCAA | GGTCACTGAGCAGCA |
| AACCACGTGGACAGC | CGGAAGCCCCTCAAG | GTCACTGAGCAGCAC |
| ACCACGTGGACAGCA | GGAAGCCCCTCAAGT | TCACTGAGCAGCACC |
| CCACGTGGACAGCAC | GAAGCCCCTCAAGTC | CACTGAGCAGCACCG |
| CACGTGGACAGCACC | AAGCCCCTCAAGTCG | ACTGAGCAGCACCGG |
| ACGTGGACAGCACCA | AGCCCCTCAAGTCGG | CTGAGCAGCACCGGC |
| CGTGGACAGCACCAT | GCCCCTCAAGTCGGG | TGAGCAGCACCGGCA |
| GTGGACAGCACCATG | CCCCTCAAGTCGGGT | GAGCAGCACCGGCAG |
| TGGACAGCACCATGA | CCCTCAAGTCGGGTA | AGCAGCACCGGCAGA |
| GGACAGCACCATGAA | CCTCAAGTCGGGTAT | GCAGCACCGGCAGAT |
| GACAGCACCATGAAC | CTCAAGTCGGGTATG | CAGCACCGGCAGATG |
| ACAGCACCATGAACA | TCAAGTCGGGTATGA | AGCACCGGCAGATGG |
| CAGCACCATGAACAT | CAAGTCGGGTATGAA | GCACCGGCAGATGGG |
| AGCACCATGAACATG | AAGTCGGGTATGAAG | CACCGGCAGATGGGC |
| GCACCATGAACATGT | AGTCGGGTATGAAGG | ACCGGCAGATGGGCA |
| CACCATGAACATGTT | GTCGGGTATGAAGGA | CCGGCAGATGGGCAA |
| ACCATGAACATGTTG | TCGGGTATGAAGGAG | CGGCAGATGGGCAAG |
| CCATGAACATGTTGG | CGGGTATGAAGGAGC | GGCAGATGGGCAAGG |
| CATGAACATGTTGGG | GGGTATGAAGGAGCT | GCAGATGGGCAAGGG |
| ATGAACATGTTGGGC | GGTATGAAGGAGCTG | CAGATGGGCAAGGGT |
| TGAACATGTTGGGCG | GTATGAAGGAGCTGG | AGATGGGCAAGGGTG |
| GAACATGTTGGGCGG | TATGAAGGAGCTGGC | GATGGGCAAGGGTGG |
| AACATGTTGGGCGGG | ATGAAGGAGCTGGCC | ATGGGCAAGGGTGGC |
| ACATGTTGGGCGGGG | TGAAGGAGCTGGCCG | TGGGCAAGGGTGGCA |
| CATGTTGGGCGGGGG | GAAGGAGCTGGCCGT | GGGCAAGGGTGGCAA |
| ATGTTGGGCGGGGGA | AAGGAGCTGGCCGTG | GGCAAGGGTGGCAAG |
| TGTTGGGCGGGGGAG | AGGAGCTGGCCGTGT | GCAAGGGTGGCAAGC |
| GTTGGGCGGGGGAGG | GGAGCTGGCCGTGTT | CAAGGGTGGCAAGCA |
| TTGGGCGGGGGAGGC | GAGCTGGCCGTGTTC | AAGGGTGGCAAGCAT |
| TGGGCGGGGGAGGCA | AGCTGGCCGTGTTCC | AGGGTGGCAAGCATC |
| GGGCGGGGGAGGCAG | GCTGGCCGTGTTCCG | GGGTGGCAAGCATCA |
| GGCGGGGGAGGCAGT | CTGGCCGTGTTCCGG | GGTGGCAAGCATCAC |
| GCGGGGGAGGCAGTG | TGGCCGTGTTCCGGG | GTGGCAAGCATCACC |
| CGGGGGAGGCAGTGC | GGCCGTGTTCCGGGA | TGGCAAGCATCACCT |
| GGGGGAGGCAGTGCT | GCCGTGTTCCGGGAG | GGCAAGCATCACCTT |
| GGGGAGGCAGTGCTG | CCGTGTTCCGGGAGA | GCAAGCATCACCTTG |
| GGGAGGCAGTGCTGG | CGTGTTCCGGGAGAA | CAAGCATCACCTTGG |
| GGAGGCAGTGCTGGC | GTGTTCCGGGAGAAG | AAGCATCACCTTGGC |
| GAGGCAGTGCTGGCC | TGTTCCGGGAGAAGG | AGCATCACCTTGGCC |
| AGGCAGTGCTGGCCG | GTTCCGGGAGAAGGT | GCATCACCTTGGCCT |
| GGCAGTGCTGGCCGG | TTCCGGGAGAAGGTC | CATCACCTTGGCCTG |
| GCAGTGCTGGCCGGA | TCCGGGAGAAGGTCA | ATCACCTTGGCCTGG |
| CAGTGCTGGCCGGAA | CCGGGAGAAGGTCAC | TCACCTTGGCCTGGA |

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|---|---|---|---|
| | CACCTTGGCCTGGAG | CCCTGCCAACAGGAA | CTTCCGGATGAGCGG |
| | ACCTTGGCCTGGAGG | CCTGCCAACAGGAAC | TTCCGGATGAGCGGG |
| | CCTTGGCCTGGAGGA | CTGCCAACAGGAACT | TCCGGATGAGCGGGG |
| | CTTGGCCTGGAGGAG | TGCCAACAGGAACTG | CCGGATGAGCGGGGC |
| 5 | TTGGCCTGGAGGAGC | GCCAACAGGAACTGG | CGGATGAGCGGGGCC |
| | TGGCCTGGAGGAGCC | CCAACAGGAACTGGA | GGATGAGCGGGGCCC |
| | GGCCTGGAGGAGCCC | CAACAGGAACTGGAC | GATGAGCGGGGCCCT |
| | GCCTGGAGGAGCCCA | AACAGGAACTGGACC | ATGAGCGGGGCCCTC |
| | CCTGGAGGAGCCCAA | ACAGGAACTGGACCA | TGAGCGGGGCCCTCT |
| 10 | CTGGAGGAGCCCAAG | CAGGAACTGGACCAG | GAGCGGGGCCCTCTG |
| | TGGAGGAGCCCAAGA | AGGAACTGGACCAGG | AGCGGGGCCCTCTGG |
| | GGAGGAGCCCAAGAA | GGAACTGGACCAGGT | GCGGGGCCCTCTGGA |
| | GAGGAGCCCAAGAAG | GAACTGGACCAGGTC | CGGGGCCCTCTGGAG |
| | AGGAGCCCAAGAAGC | AACTGGACCAGGTCC | GGGGCCCTCTGGAGC |
| 15 | GGAGCCCAAGAAGCT | ACTGGACCAGGTCCT | GGGCCCTCTGGAGCA |
| | GAGCCCAAGAAGCTG | CTGGACCAGGTCCTG | GGCCCTCTGGAGCAC |
| | AGCCCAAGAAGCTGC | TGGACCAGGTCCTGG | GCCCTCTGGAGCACC |
| | GCCCAAGAAGCTGCG | GGACCAGGTCCTGGA | CCCTCTGGAGCACCT |
| | CCCAAGAAGCTGCGA | GACCAGGTCCTGGAG | CCTCTGGAGCACCTC |
| 20 | CCAAGAAGCTGCGAC | ACCAGGTCCTGGAGC | CTCTGGAGCACCTCT |
| | CAAGAAGCTGCGACC | CCAGGTCCTGGAGCG | TCTGGAGCACCTCTA |
| | AAGAAGCTGCGACCA | CAGGTCCTGGAGCGG | CTGGAGCACCTCTAC |
| | AGAAGCTGCGACCAC | AGGTCCTGGAGCGGA | TGGAGCACCTCTACT |
| | GAAGCTGCGACCACC | GGTCCTGGAGCGGAT | GGAGCACCTCTACTC |
| 25 | AAGCTGCGACCACCC | GTCCTGGAGCGGATC | GAGCACCTCTACTCC |
| | AGCTGCGACCACCCC | TCCTGGAGCGGATCT | AGCACCTCTACTCCC |
| | GCTGCGACCACCCCC | CCTGGAGCGGATCTC | GCACCTCTACTCCCT |
| | CTGCGACCACCCCCT | CTGGAGCGGATCTCC | CACCTCTACTCCCTG |
| | TGCGACCACCCCCTG | TGGAGCGGATCTCCA | ACCTCTACTCCCTGC |
| 30 | GCGACCACCCCCTGC | GGAGCGGATCTCCAC | CCTCTACTCCCTGCA |
| | CGACCACCCCCTGCC | GAGCGGATCTCCACC | CTCTACTCCCTGCAC |
| | GACCACCCCCTGCCA | AGCGGATCTCCACCA | TCTACTCCCTGCACA |
| | ACCACCCCCTGCCAG | GCGGATCTCCACCAT | CTACTCCCTGCACAT |
| | CCACCCCCTGCCAGG | CGGATCTCCACCATG | TACTCCCTGCACATC |
| 35 | CACCCCCTGCCAGGA | GGATCTCCACCATGC | ACTCCCTGCACATCC |
| | ACCCCCTGCCAGGAC | GATCTCCACCATGCG | CTCCCTGCACATCCC |
| | CCCCCTGCCAGGACT | ATCTCCACCATGCGC | TCCCTGCACATCCCC |
| | CCCCTGCCAGGACTC | TCTCCACCATGCGCC | CCCTGCACATCCCCA |
| | CCCTGCCAGGACTCC | CTCCACCATGCGCCT | CCTGCACATCCCCAA |
| 40 | CCTGCCAGGACTCCC | TCCACCATGCGCCTT | CTGCACATCCCCAAC |
| | CTGCCAGGACTCCCT | CCACCATGCGCCTTC | TGCACATCCCCAACT |
| | TGCCAGGACTCCCTG | CACCATGCGCCTTCC | GCACATCCCCAACTG |
| | GCCAGGACTCCCTGC | ACCATGCGCCTTCCG | CACATCCCCAACTGT |
| | CCAGGACTCCCTGCC | CCATGCGCCTTCCGG | ACATCCCCAACTGTG |
| 45 | CAGGACTCCCTGCCA | CATGCGCCTTCCGGA | CATCCCCAACTGTGA |
| | AGGACTCCCTGCCAA | ATGCGCCTTCCGGAT | ATCCCCAACTGTGAC |
| | GGACTCCCTGCCAAC | TGCGCCTTCCGGATG | TCCCCAACTGTGACA |
| | GACTCCCTGCCAACA | GCGCCTTCCGGATGA | CCCCAACTGTGACAA |
| | ACTCCCTGCCAACAG | CGCCTTCCGGATGAG | CCCAACTGTGACAAG |
| 50 | CTCCCTGCCAACAGG | GCCTTCCGGATGAGC | CCAACTGTGACAAGC |
| | TCCCTGCCAACAGGA | CCTTCCGGATGAGCG | CAACTGTGACAAGCA |

| | | |
|---|---|---|
| AACTGTGACAAGCAT | AACGGGCAGCGTGGG | ATCCAGGGAGCCCCC |
| ACTGTGACAAGCATG | ACGGGCAGCGTGGGG | TCCAGGGAGCCCCCA |
| CTGTGACAAGCATGG | CGGGCAGCGTGGGGA | CCAGGGAGCCCCCAC |
| TGTGACAAGCATGGC | GGGCAGCGTGGGGAG | CAGGGAGCCCCCACC |
| GTGACAAGCATGGCC | GGCAGCGTGGGGAGT | AGGGAGCCCCCACCA |
| TGACAAGCATGGCCT | GCAGCGTGGGGAGTG | GGGAGCCCCCACCAT |
| GACAAGCATGGCCTG | CAGCGTGGGGAGTGC | GGAGCCCCCACCATC |
| ACAAGCATGGCCTGT | AGCGTGGGGAGTGCT | GAGCCCCCACCATCC |
| CAAGCATGGCCTGTA | GCGTGGGGAGTGCTG | AGCCCCCACCATCCG |
| AAGCATGGCCTGTAC | CGTGGGGAGTGCTGG | GCCCCCACCATCCGG |
| AGCATGGCCTGTACA | GTGGGGAGTGCTGGT | CCCCCACCATCCGGG |
| GCATGGCCTGTACAA | TGGGGAGTGCTGGTG | CCCCACCATCCGGGG |
| CATGGCCTGTACAAC | GGGGAGTGCTGGTGT | CCCACCATCCGGGGG |
| ATGGCCTGTACAACC | GGGAGTGCTGGTGTG | CCACCATCCGGGGGG |
| TGGCCTGTACAACCT | GGAGTGCTGGTGTGT | CACCATCCGGGGGGA |
| GGCCTGTACAACCTC | GAGTGCTGGTGTGTG | ACCATCCGGGGGGAC |
| GCCTGTACAACCTCA | AGTGCTGGTGTGTGA | CCATCCGGGGGGACC |
| CCTGTACAACCTCAA | GTGCTGGTGTGTGAA | CATCCGGGGGGACCC |
| CTGTACAACCTCAAA | TGCTGGTGTGTGAAC | ATCCGGGGGGACCCC |
| TGTACAACCTCAAAC | GCTGGTGTGTGAACC | TCCGGGGGGACCCCG |
| GTACAACCTCAAACA | CTGGTGTGTGAACCC | CCGGGGGGACCCCGA |
| TACAACCTCAAACAG | TGGTGTGTGAACCCC | CGGGGGGACCCCGAG |
| ACAACCTCAAACAGT | GGTGTGTGAACCCCA | GGGGGGACCCCGAGT |
| CAACCTCAAACAGTG | GTGTGTGAACCCCAA | GGGGGACCCCGAGTG |
| AACCTCAAACAGTGC | TGTGTGAACCCCAAC | GGGGACCCCGAGTGT |
| ACCTCAAACAGTGCA | GTGTGAACCCCAACA | GGGACCCCGAGTGTC |
| CCTCAAACAGTGCAA | TGTGAACCCCAACAC | GGACCCCGAGTGTCA |
| CTCAAACAGTGCAAG | GTGAACCCCAACACC | GACCCCGAGTGTCAT |
| TCAAACAGTGCAAGA | TGAACCCCAACACCG | ACCCCGAGTGTCATC |
| CAAACAGTGCAAGAT | GAACCCCAACACCGG | CCCCGAGTGTCATCT |
| AAACAGTGCAAGATG | AACCCCAACACCGGG | CCCGAGTGTCATCTC |
| AACAGTGCAAGATGT | ACCCCAACACCGGGA | CCGAGTGTCATCTCT |
| ACAGTGCAAGATGTC | CCCCAACACCGGGAA | CGAGTGTCATCTCTT |
| CAGTGCAAGATGTCT | CCCAACACCGGGAAG | GAGTGTCATCTCTTC |
| AGTGCAAGATGTCTC | CCAACACCGGGAAGC | AGTGTCATCTCTTCT |
| GTGCAAGATGTCTCT | CAACACCGGGAAGCT | GTGTCATCTCTTCTA |
| TGCAAGATGTCTCTG | AACACCGGGAAGCTG | TGTCATCTCTTCTAC |
| GCAAGATGTCTCTGA | ACACCGGGAAGCTGA | GTCATCTCTTCTACA |
| CAAGATGTCTCTGAA | CACCGGGAAGCTGAT | TCATCTCTTCTACAA |
| AAGATGTCTCTGAAC | ACCGGGAAGCTGATC | CATCTCTTCTACAAT |
| AGATGTCTCTGAACG | CCGGGAAGCTGATCC | ATCTCTTCTACAATG |
| GATGTCTCTGAACGG | CGGGAAGCTGATCCA | TCTCTTCTACAATGA |
| ATGTCTCTGAACGGG | GGGAAGCTGATCCAG | CTCTTCTACAATGAG |
| TGTCTCTGAACGGGC | GGAAGCTGATCCAGG | TCTTCTACAATGAGC |
| GTCTCTGAACGGGCA | GAAGCTGATCCAGGG | CTTCTACAATGAGCA |
| TCTCTGAACGGGCAG | AAGCTGATCCAGGGA | TTCTACAATGAGCAG |
| CTCTGAACGGGCAGC | AGCTGATCCAGGGAG | TCTACAATGAGCAGC |
| TCTGAACGGGCAGCG | GCTGATCCAGGGAGC | CTACAATGAGCAGCA |
| CTGAACGGGCAGCGT | CTGATCCAGGGAGCC | TACAATGAGCAGCAG |
| TGAACGGGCAGCGTG | TGATCCAGGGAGCCC | ACAATGAGCAGCAGG |
| GAACGGGCAGCGTGG | GATCCAGGGAGCCCC | CAATGAGCAGCAGGA |

| | | | |
|---|---|---|---|
| | AATGAGCAGCAGGAG | GCAGCCAGCCGGTGC | GCAGAAAACGGAGAG |
| | ATGAGCAGCAGGAGG | CAGCCAGCCGGTGCC | CAGAAAACGGAGAGT |
| | TGAGCAGCAGGAGGC | AGCCAGCCGGTGCCT | AGAAAACGGAGAGTG |
| | GAGCAGCAGGAGGCT | GCCAGCCGGTGCCTG | GAAAACGGAGAGTGC |
| 5 | AGCAGCAGGAGGCTT | CCAGCCGGTGCCTGG | AAAACGGAGAGTGCT |
| | GCAGCAGGAGGCTTG | CAGCCGGTGCCTGGC | AAACGGAGAGTGCTT |
| | CAGCAGGAGGCTTGC | AGCCGGTGCCTGGCG | AACGGAGAGTGCTTG |
| | AGCAGGAGGCTTGCG | GCCGGTGCCTGGCGC | ACGGAGAGTGCTTGG |
| | GCAGGAGGCTTGCGG | CCGGTGCCTGGCGCC | CGGAGAGTGCTTGGG |
| 10 | CAGGAGGCTTGCGGG | CGGTGCCTGGCGCCC | GGAGAGTGCTTGGGT |
| | AGGAGGCTTGCGGGG | GGTGCCTGGCGCCCC | GAGAGTGCTTGGGTG |
| | GGAGGCTTGCGGGGT | GTGCCTGGCGCCCCT | AGAGTGCTTGGGTGG |
| | GAGGCTTGCGGGGTG | TGCCTGGCGCCCCTG | GAGTGCTTGGGTGGT |
| | AGGCTTGCGGGGTGC | GCCTGGCGCCCCTGC | AGTGCTTGGGTGGTG |
| 15 | GGCTTGCGGGGTGCA | CCTGGCGCCCCTGCC | GTGCTTGGGTGGTGG |
| | GCTTGCGGGGTGCAC | CTGGCGCCCCTGCCC | TGCTTGGGTGGTGGG |
| | CTTGCGGGGTGCACA | TGGCGCCCCTGCCCC | GCTTGGGTGGTGGGT |
| | TTGCGGGGTGCACAC | GGCGCCCCTGCCCCC | CTTGGGTGGTGGGTG |
| | TGCGGGGTGCACACC | GCGCCCCTGCCCCCC | TTGGGTGGTGGGTGC |
| 20 | GCGGGGTGCACACCC | CGCCCCTGCCCCCCG | TGGGTGGTGGGTGCT |
| | CGGGGTGCACACCCA | GCCCCTGCCCCCCGC | GGGTGGTGGGTGCTG |
| | GGGGTGCACACCCAG | CCCCTGCCCCCCGCC | GGTGGTGGGTGCTGG |
| | GGGTGCACACCCAGC | CCCTGCCCCCCGCCC | GTGGTGGGTGCTGGA |
| | GGTGCACACCCAGCG | CCTGCCCCCCGCCCC | TGGTGGGTGCTGGAG |
| 25 | GTGCACACCCAGCGG | CTGCCCCCCGCCCCT | GGTGGGTGCTGGAGG |
| | TGCACACCCAGCGGA | TGCCCCCCGCCCCTC | GTGGGTGCTGGAGGA |
| | GCACACCCAGCGGAT | GCCCCCCGCCCCTCT | TGGGTGCTGGAGGAT |
| | CACACCCAGCGGATG | CCCCCCGCCCCTCTC | GGGTGCTGGAGGATT |
| | ACACCCAGCGGATGC | CCCCCGCCCCTCTCC | GGTGCTGGAGGATTT |
| 30 | CACCCAGCGGATGCA | CCCCGCCCCTCTCCA | GTGCTGGAGGATTTT |
| | ACCCAGCGGATGCAG | CCCGCCCCTCTCCAA | TGCTGGAGGATTTTC |
| | CCCAGCGGATGCAGT | CCGCCCCTCTCCAAA | GCTGGAGGATTTTCC |
| | CCAGCGGATGCAGTA | CGCCCCTCTCCAAAC | CTGGAGGATTTTCCA |
| | CAGCGGATGCAGTAG | GCCCCTCTCCAAACA | TGGAGGATTTTCCAG |
| 35 | AGCGGATGCAGTAGA | CCCCTCTCCAAACAC | GGAGGATTTTCCAGT |
| | GCGGATGCAGTAGAC | CCCTCTCCAAACACC | GAGGATTTTCCAGTT |
| | CGGATGCAGTAGACC | CCTCTCCAAACACCG | AGGATTTTCCAGTTC |
| | GGATGCAGTAGACCG | CTCTCCAAACACCGG | GGATTTTCCAGTTCT |
| | GATGCAGTAGACCGC | TCTCCAAACACCGGC | GATTTTCCAGTTCTG |
| 40 | ATGCAGTAGACCGCA | CTCCAAACACCGGCA | ATTTTCCAGTTCTGA |
| | TGCAGTAGACCGCAG | TCCAAACACCGGCAG | TTTTCCAGTTCTGAC |
| | GCAGTAGACCGCAGC | CCAAACACCGGCAGA | TTTCCAGTTCTGACA |
| | CAGTAGACCGCAGCC | CAAACACCGGCAGAA | TTCCAGTTCTGACAC |
| | AGTAGACCGCAGCCA | AAACACCGGCAGAAA | TCCAGTTCTGACACA |
| 45 | GTAGACCGCAGCCAG | AACACCGGCAGAAAA | CCAGTTCTGACACAC |
| | TAGACCGCAGCCAGC | ACACCGGCAGAAAAC | CAGTTCTGACACACG |
| | AGACCGCAGCCAGCC | CACCGGCAGAAAACG | AGTTCTGACACACGT |
| | GACCGCAGCCAGCCG | ACCGGCAGAAAACGG | GTTCTGACACACGTA |
| | ACCGCAGCCAGCCGG | CCGGCAGAAAACGGA | TTCTGACACACGTAT |
| 50 | CCGCAGCCAGCCGGT | CGGCAGAAAACGGAG | TCTGACACACGTATT |
| | CGCAGCCAGCCGGTG | GGCAGAAAACGGAGA | CTGACACACGTATTT |

| | | | |
|---|---|---|---|
| | TGACACACGTATTTA | CCCGGCCTCTCTCTT | TCCCCGGGGGAGGAA |
| | GACACACGTATTTAT | CCGGCCTCTCTCTTC | CCCCGGGGGAGGAAG |
| | ACACACGTATTTATA | CGGCCTCTCTCTTCC | CCCGGGGGAGGAAGG |
| | CACACGTATTTATAT | GGCCTCTCTCTTCCC | CCGGGGGAGGAAGGG |
| 5 | ACACGTATTTATATT | GCCTCTCTCTTCCCA | CGGGGGAGGAAGGGG |
| | CACGTATTTATATTT | CCTCTCTCTTCCCAG | GGGGGAGGAAGGGGG |
| | ACGTATTTATATTTG | CTCTCTCTTCCCAGC | GGGGAGGAAGGGGGT |
| | CGTATTTATATTTGG | TCTCTCTTCCCAGCT | GGGAGGAAGGGGGTT |
| | GTATTTATATTTGGA | CTCTCTTCCCAGCTG | GGAGGAAGGGGGTTG |
| 10 | TATTTATATTTGGAA | TCTCTTCCCAGCTGC | GAGGAAGGGGGTTGT |
| | ATTTATATTTGGAAA | CTCTTCCCAGCTGCA | AGGAAGGGGGTTGTG |
| | TTTATATTTGGAAAG | TCTTCCCAGCTGCAG | GGAAGGGGGTTGTGG |
| | TTATATTTGGAAAGA | CTTCCCAGCTGCAGA | GAAGGGGGTTGTGGT |
| | TATATTTGGAAAGAG | TTCCCAGCTGCAGAT | AAGGGGGTTGTGGTC |
| 15 | ATATTTGGAAAGAGA | TCCCAGCTGCAGATG | AGGGGGTTGTGGTCG |
| | TATTTGGAAAGAGAC | CCCAGCTGCAGATGC | GGGGGTTGTGGTCGG |
| | ATTTGGAAAGAGACC | CCAGCTGCAGATGCC | GGGGTTGTGGTCGGG |
| | TTTGGAAAGAGACCA | CAGCTGCAGATGCCA | GGGTTGTGGTCGGGG |
| | TTGGAAAGAGACCAG | AGCTGCAGATGCCAC | GGTTGTGGTCGGGGA |
| 20 | TGGAAAGAGACCAGC | GCTGCAGATGCCACA | GTTGTGGTCGGGGAG |
| | GGAAAGAGACCAGCA | CTGCAGATGCCACAC | TTGTGGTCGGGGAGC |
| | GAAAGAGACCAGCAC | TGCAGATGCCACACC | TGTGGTCGGGGAGCT |
| | AAAGAGACCAGCACC | GCAGATGCCACACCT | GTGGTCGGGGAGCTG |
| | AAGAGACCAGCACCG | CAGATGCCACACCTG | TGGTCGGGGAGCTGG |
| 25 | AGAGACCAGCACCGA | AGATGCCACACCTGC | GGTCGGGGAGCTGGG |
| | GAGACCAGCACCGAG | GATGCCACACCTGCT | GTCGGGGAGCTGGGG |
| | AGACCAGCACCGAGC | ATGCCACACCTGCTC | TCGGGGAGCTGGGGT |
| | GACCAGCACCGAGCT | TGCCACACCTGCTCC | CGGGGAGCTGGGGTA |
| | ACCAGCACCGAGCTC | GCCACACCTGCTCCT | GGGGAGCTGGGGTAC |
| 30 | CCAGCACCGAGCTCG | CCACACCTGCTCCTT | GGGAGCTGGGGTACA |
| | CAGCACCGAGCTCGG | CACACCTGCTCCTTC | GGAGCTGGGGTACAG |
| | AGCACCGAGCTCGGC | ACACCTGCTCCTTCT | GAGCTGGGGTACAGG |
| | GCACCGAGCTCGGCA | CACCTGCTCCTTCTT | AGCTGGGGTACAGGT |
| | CACCGAGCTCGGCAC | ACCTGCTCCTTCTTG | GCTGGGGTACAGGTT |
| 35 | ACCGAGCTCGGCACC | CCTGCTCCTTCTTGC | CTGGGGTACAGGTTT |
| | CCGAGCTCGGCACCT | CTGCTCCTTCTTGCT | TGGGGTACAGGTTTG |
| | CGAGCTCGGCACCTC | TGCTCCTTCTTGCTT | GGGGTACAGGTTTGG |
| | GAGCTCGGCACCTCC | GCTCCTTCTTGCTTT | GGGTACAGGTTTGGG |
| | AGCTCGGCACCTCCC | CTCCTTCTTGCTTTC | GGTACAGGTTTGGGG |
| 40 | GCTCGGCACCTCCCC | TCCTTCTTGCTTTCC | GTACAGGTTTGGGGA |
| | CTCGGCACCTCCCCG | CCTTCTTGCTTTCCC | TACAGGTTTGGGGAG |
| | TCGGCACCTCCCCGG | CTTCTTGCTTTCCCC | ACAGGTTTGGGGAGG |
| | CGGCACCTCCCCGGC | TTCTTGCTTTCCCCG | CAGGTTTGGGGAGGG |
| | GGCACCTCCCCGGCC | TCTTGCTTTCCCCGG | AGGTTTGGGGAGGGG |
| 45 | GCACCTCCCCGGCCT | CTTGCTTTCCCCGGG | GGTTTGGGGAGGGGG |
| | CACCTCCCCGGCCTC | TTGCTTTCCCCGGGG | GTTTGGGGAGGGGGA |
| | ACCTCCCCGGCCTCT | TGCTTTCCCCGGGGG | TTTGGGGAGGGGGAA |
| | CCTCCCCGGCCTCTC | GCTTTCCCCGGGGGA | TTGGGGAGGGGGAAG |
| | CTCCCCGGCCTCTCT | CTTTCCCCGGGGGAG | TGGGGAGGGGGAAGA |
| 50 | TCCCCGGCCTCTCTC | TTTCCCCGGGGGAGG | GGGGAGGGGGAAGAG |
| | CCCCGGCCTCTCTCT | TTCCCCGGGGGAGGA | GGGAGGGGGAAGAGA |

| | | |
|---|---|---|
| | GGAGGGGGAAGAGAA | AGATTAAAGGAAGGA |
| | GAGGGGGAAGAGAAA | GATTAAAGGAAGGAA |
| | AGGGGGAAGAGAAAT | ATTAAAGGAAGGAAA |
| | GGGGGAAGAGAAATT | TTAAAGGAAGGAAAA |
| 5 | GGGGAAGAGAAATTT | TAAAGGAAGGAAAAG |
| | GGGAAGAGAAATTTT | AAAGGAAGGAAAAGT |
| | GGAAGAGAAATTTTT | |
| | GAAGAGAAATTTTTA | |
| | AAGAGAAATTTTTAT | |
| 10 | AGAGAAATTTTTATT | |
| | GAGAAATTTTTATTT | |
| | AGAAATTTTTATTTT | |
| | GAAATTTTTATTTTT | |
| | AAATTTTTATTTTTG | |
| 15 | AATTTTTATTTTTGA | |
| | ATTTTTATTTTTGAA | |
| | TTTTTATTTTTGAAC | |
| | TTTTATTTTTGAACC | |
| | TTTATTTTTGAACCC | |
| 20 | TTATTTTTGAACCCC | |
| | TATTTTTGAACCCCT | |
| | ATTTTTGAACCCCTG | |
| | TTTTTGAACCCCTGT | |
| | TTTTGAACCCCTGTG | |
| 25 | TTTGAACCCCTGTGT | |
| | TTGAACCCCTGTGTC | |
| | TGAACCCCTGTGTCC | |
| | GAACCCCTGTGTCCC | |
| | AACCCCTGTGTCCCT | |
| 30 | ACCCCTGTGTCCCTT | |
| | CCCCTGTGTCCCTTT | |
| | CCCTGTGTCCCTTTT | |
| | CCTGTGTCCCTTTTG | |
| | CTGTGTCCCTTTTGC | |
| 35 | TGTGTCCCTTTTGCA | |
| | GTGTCCCTTTTGCAT | |
| | TGTCCCTTTTGCATA | |
| | GTCCCTTTTGCATAA | |
| | TCCCTTTTGCATAAG | |
| 40 | CCCTTTTGCATAAGA | |
| | CCTTTTGCATAAGAT | |
| | CTTTTGCATAAGATT | |
| | TTTTGCATAAGATTA | |
| | TTTGCATAAGATTAA | |
| 45 | TTGCATAAGATTAAA | |
| | TGCATAAGATTAAAG | |
| | GCATAAGATTAAAGG | |
| | CATAAGATTAAAGGA | |
| | ATAAGATTAAAGGAA | |
| 50 | TAAGATTAAAGGAAG | |
| | AAGATTAAAGGAAGG | |

## EXAMPLE 7

Antisense oligonucleotides to IGFBP3 may be selected from molecules capable of interacting with one or more of the following sense oligonucleotides:

| | | |
|---|---|---|
| CTCAGCGCCCAGCCG | GCCGTGTACTGTCGC | GCAGCGTGCCCCGGT |
| TCAGCGCCCAGCCGC | CCGTGTACTGTCGCC | CAGCGTGCCCCGGTT |
| CAGCGCCCAGCCGCT | CGTGTACTGTCGCCC | AGCGTGCCCCGGTTG |
| AGCGCCCAGCCGCTT | GTGTACTGTCGCCCC | GCGTGCCCCGGTTGC |
| GCGCCCAGCCGCTTC | TGTACTGTCGCCCCA | CGTGCCCCGGTTGCA |
| CGCCCAGCCGCTTCC | GTACTGTCGCCCCAT | GTGCCCCGGTTGCAG |
| GCCCAGCCGCTTCCT | TACTGTCGCCCCATC | TGCCCCGGTTGCAGG |
| CCCAGCCGCTTCCTG | ACTGTCGCCCCATCC | GCCCCGGTTGCAGGC |
| CCAGCCGCTTCCTGC | CTGTCGCCCCATCCC | CCCCGGTTGCAGGCG |
| CAGCCGCTTCCTGCC | TGTCGCCCCATCCCT | CCCGGTTGCAGGCGT |
| AGCCGCTTCCTGCCT | GTCGCCCCATCCCTG | CCGGTTGCAGGCGTC |
| GCCGCTTCCTGCCTG | TCGCCCCATCCCTGC | CGGTTGCAGGCGTCA |
| CCGCTTCCTGCCTGG | CGCCCCATCCCTGCG | GGTTGCAGGCGTCAT |
| CGCTTCCTGCCTGGA | GCCCCATCCCTGCGC | GTTGCAGGCGTCATG |
| GCTTCCTGCCTGGAT | CCCCATCCCTGCGCG | TTGCAGGCGTCATGC |
| CTTCCTGCCTGGATT | CCCATCCCTGCGCGC | TGCAGGCGTCATGCA |
| TTCCTGCCTGGATTC | CCATCCCTGCGCGCC | GCAGGCGTCATGCAG |
| TCCTGCCTGGATTCC | CATCCCTGCGCGCCC | CAGGCGTCATGCAGC |
| CCTGCCTGGATTCCA | ATCCCTGCGCGCCCA | AGGCGTCATGCAGCG |
| CTGCCTGGATTCCAC | TCCCTGCGCGCCCAG | GGCGTCATGCAGCGG |
| TGCCTGGATTCCACA | CCCTGCGCGCCCAGC | GCGTCATGCAGCGGG |
| GCCTGGATTCCACAG | CCTGCGCGCCCAGCC | CGTCATGCAGCGGGC |
| CCTGGATTCCACAGC | CTGCGCGCCCAGCCT | GTCATGCAGCGGGCG |
| CTGGATTCCACAGCT | TGCGCGCCCAGCCTG | TCATGCAGCGGGCGC |
| TGGATTCCACAGCTT | GCGCGCCCAGCCTGC | CATGCAGCGGGCGCG |
| GGATTCCACAGCTTC | CGCGCCCAGCCTGCC | ATGCAGCGGGCGCGA |
| GATTCCACAGCTTCG | GCGCCCAGCCTGCCA | TGCAGCGGGCGCGAC |
| ATTCCACAGCTTCGC | CGCCCAGCCTGCCAA | GCAGCGGGCGCGACC |
| TTCCACAGCTTCGCG | GCCCAGCCTGCCAAG | CAGCGGGCGCGACCC |
| TCCACAGCTTCGCGC | CCCAGCCTGCCAAGC | AGCGGGCGCGACCCA |
| CCACAGCTTCGCGCC | CCAGCCTGCCAAGCA | GCGGGCGCGACCCAC |
| CACAGCTTCGCGCCG | CAGCCTGCCAAGCAG | CGGGCGCGACCCACG |
| ACAGCTTCGCGCCGT | AGCCTGCCAAGCAGC | GGGCGCGACCCACGC |
| CAGCTTCGCGCCGTG | GCCTGCCAAGCAGCG | GGCGCGACCCACGCT |
| AGCTTCGCGCCGTGT | CCTGCCAAGCAGCGT | GCGCGACCCACGCTC |
| GCTTCGCGCCGTGTA | CTGCCAAGCAGCGTG | CGCGACCCACGCTCT |
| CTTCGCGCCGTGTAC | TGCCAAGCAGCGTGC | GCGACCCACGCTCTG |
| TTCGCGCCGTGTACT | GCCAAGCAGCGTGCC | CGACCCACGCTCTGG |
| TCGCGCCGTGTACTG | CCAAGCAGCGTGCCC | GACCCACGCTCTGGG |
| CGCGCCGTGTACTGT | CAAGCAGCGTGCCCC | ACCCACGCTCTGGGC |
| GCGCCGTGTACTGTC | AAGCAGCGTGCCCCG | CCCACGCTCTGGGCC |
| CGCCGTGTACTGTCG | AGCAGCGTGCCCCGG | CCACGCTCTGGGCCG |

| | | |
|---|---|---|
| CACGCTCTGGGCCGC | GGTGGCGCGGGCTGG | CGAGCCGTGCGACGC |
| ACGCTCTGGGCCGCT | GTGGCGCGGGCTGGC | GAGCCGTGCGACGCG |
| CGCTCTGGGCCGCTG | TGGCGCGGGCTGGCG | AGCCGTGCGACGCGC |
| GCTCTGGGCCGCTGC | GGCGCGGGCTGGCGC | GCCGTGCGACGCGCG |
| CTCTGGGCCGCTGCG | GCGCGGGCTGGCGCG | CCGTGCGACGCGCGT |
| TCTGGGCCGCTGCGC | CGCGGGCTGGCGCGA | CGTGCGACGCGCGTG |
| CTGGGCCGCTGCGCT | GCGGGCTGGCGCGAG | GTGCGACGCGCGTGC |
| TGGGCCGCTGCGCTG | CGGGCTGGCGCGAGC | TGCGACGCGCGTGCA |
| GGGCCGCTGCGCTGA | GGGCTGGCGCGAGCT | GCGACGCGCGTGCAC |
| GGCCGCTGCGCTGAC | GGCTGGCGCGAGCTC | CGACGCGCGTGCACT |
| GCCGCTGCGCTGACT | GCTGGCGCGAGCTCG | GACGCGCGTGCACTG |
| CCGCTGCGCTGACTC | CTGGCGCGAGCTCGG | ACGCGCGTGCACTGG |
| CGCTGCGCTGACTCT | TGGCGCGAGCTCGGG | CGCGCGTGCACTGGC |
| GCTGCGCTGACTCTG | GGCGCGAGCTCGGGG | GCGCGTGCACTGGCC |
| CTGCGCTGACTCTGC | GCGCGAGCTCGGGGG | CGCGTGCACTGGCCC |
| TGCGCTGACTCTGCT | CGCGAGCTCGGGGGG | GCGTGCACTGGCCCA |
| GCGCTGACTCTGCTG | GCGAGCTCGGGGGGC | CGTGCACTGGCCCAG |
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| GCTGACTCTGCTGGT | GAGCTCGGGGGGCTT | TGCACTGGCCCAGTG |
| CTGACTCTGCTGGTG | AGCTCGGGGGGCTTG | GCACTGGCCCAGTGC |
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| CTGCTCCGCGGGCCG | GGTCCCGTGGTGCGC | GCGCCTCCGCCCGCC |
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| CGGTGGCGCGGGCTG | GCGAGCCGTGCGACG | TGTGCGCGGAGCTGG |

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| | AGCTGGTGCGCGAGC | AGGGCCAGCCGTGCG | GCCAGCCGTCGCCCG |
| 10 | GCTGGTGCGCGAGCC | GGGCCAGCCGTGCGG | CCAGCCGTCGCCCGA |
| | CTGGTGCGCGAGCCG | GGCCAGCCGTGCGGC | CAGCCGTCGCCCGAC |
| | TGGTGCGCGAGCCGG | GCCAGCCGTGCGGCA | AGCCGTCGCCCGACG |
| | GGTGCGCGAGCCGGG | CCAGCCGTGCGGCAT | GCCGTCGCCCGACGA |
| | GTGCGCGAGCCGGGC | CAGCCGTGCGGCATC | CCGTCGCCCGACGAG |
| 15 | TGCGCGAGCCGGGCT | AGCCGTGCGGCATCT | CGTCGCCCGACGAGG |
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| | CGCGAGCCGGGCTGC | CCGTGCGGCATCTAC | TCGCCCGACGAGGCG |
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| 20 | GAGCCGGGCTGCGGC | TGCGGCATCTACACC | CCCGACGAGGCGCGA |
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| | GCCGGGCTGCGGCTG | CGGCATCTACACCGA | CGACGAGGCGCGACC |
| | CCGGGCTGCGGCTGC | GGCATCTACACCGAG | GACGAGGCGCGACCG |
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| 30 | GCGGCTGCTGCCTGA | ACACCGAGCGCTGTG | CGCGACCGCTGCAGG |
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| 35 | TGCTGCCTGACGTGC | GAGCGCTGTGGCTCC | CCGCTGCAGGCGCTG |
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| 40 | CCTGACGTGCGCACT | CTGTGGCTCCGGCCT | GCAGGCGCTGCTGGA |
| | CTGACGTGCGCACTG | TGTGGCTCCGGCCTT | CAGGCGCTGCTGGAC |
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| | ACGTGCGCACTGAGC | GGCTCCGGCCTTCGC | GCGCTGCTGGACGGC |
| 45 | CGTGCGCACTGAGCG | GCTCCGGCCTTCGCT | CGCTGCTGGACGGCC |
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| | TGCGCACTGAGCGAG | TCCGGCCTTCGCTGC | CTGCTGGACGGCCGC |
| | GCGCACTGAGCGAGG | CCGGCCTTCGCTGCC | TGCTGGACGGCCGCG |
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| 50 | GCACTGAGCGAGGGC | GGCCTTCGCTGCCAG | CTGGACGGCCGCGGG |
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|---|---|---|
| GGACGGCCGCGGGCT | CTACCTGCTGCCAGC | AGACCGCAGCGCCGG |
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| CGGCCGCGGGCTCTG | CCTGCTGCCAGCGCC | CCGCAGCGCCGGCAG |
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| CCGCGGGCTCTGCGT | GCTGCCAGCGCCGCC | CAGCGCCGGCAGTGT |
| CGCGGGCTCTGCGTC | CTGCCAGCGCCGCCA | AGCGCCGGCAGTGTG |
| GCGGGCTCTGCGTCA | TGCCAGCGCCGCCAG | GCGCCGGCAGTGTGG |
| CGGGCTCTGCGTCAA | GCCAGCGCCGCCAGC | CGCCGGCAGTGTGGA |
| GGGCTCTGCGTCAAC | CCAGCGCCGCCAGCT | GCCGGCAGTGTGGAG |
| GGCTCTGCGTCAACG | CAGCGCCGCCAGCTC | CCGGCAGTGTGGAGA |
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| TCTGCGTCAACGCTA | CGCCGCCAGCTCCAG | GCAGTGTGGAGAGCC |
| CTGCGTCAACGCTAG | GCCGCCAGCTCCAGG | CAGTGTGGAGAGCCC |
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| AACGCTAGTGCCGTC | GCTCCAGGAAATGCT | GAGAGCCCGTCCGTC |
| ACGCTAGTGCCGTCA | CTCCAGGAAATGCTA | AGAGCCCGTCCGTCT |
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| TAGTGCCGTCAGCCG | AGGAAATGCTAGTGA | CCCGTCCGTCTCCAG |
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| 5 | TCTGATCCCAAGTTC | GGGCATGCTAAAGAC | ACAGATACCCAGAAC |
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| | TGATCCCAAGTTCCA | GCATGCTAAAGACAG | AGATACCCAGAACTT |
| | GATCCCAAGTTCCAC | CATGCTAAAGACAGC | GATACCCAGAACTTC |
| | ATCCCAAGTTCCACC | ATGCTAAAGACAGCC | ATACCCAGAACTTCT |
| 10 | TCCCAAGTTCCACCC | TGCTAAAGACAGCCA | TACCCAGAACTTCTC |
| | CCCAAGTTCCACCCC | GCTAAAGACAGCCAG | ACCCAGAACTTCTCC |
| | CCAAGTTCCACCCCC | CTAAAGACAGCCAGC | CCCAGAACTTCTCCT |
| | CAAGTTCCACCCCCT | TAAAGACAGCCAGCG | CCAGAACTTCTCCTC |
| | AAGTTCCACCCCCTC | AAAGACAGCCAGCGC | CAGAACTTCTCCTCC |
| 15 | AGTTCCACCCCCTCC | AAGACAGCCAGCGCT | AGAACTTCTCCTCCG |
| | GTTCCACCCCCTCCA | AGACAGCCAGCGCTA | GAACTTCTCCTCCGA |
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| 20 | CACCCCCTCCATTCA | AGCCAGCGCTACAAA | TTCTCCTCCGAGTCC |
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| | CCCCTCCATTCAAAG | CAGCGCTACAAAGTT | TCCTCCGAGTCCAAG |
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| 25 | CCTCCATTCAAAGAT | GCGCTACAAAGTTGA | CTCCGAGTCCAAGCG |
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| 30 | ATTCAAAGATAATCA | ACAAAGTTGACTACG | AGTCCAAGCGGGAGA |
| | TTCAAAGATAATCAT | CAAAGTTGACTACGA | GTCCAAGCGGGAGAC |
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| | CAAAGATAATCATCA | AAGTTGACTACGAGT | CCAAGCGGGAGACAG |
| | AAAGATAATCATCAT | AGTTGACTACGAGTC | CAAGCGGGAGACAGA |
| 35 | AAGATAATCATCATC | GTTGACTACGAGTCT | AAGCGGGAGACAGAA |
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| 40 | AATCATCATCAAGAA | CTACGAGTCTCAGAG | GGAGACAGAATATGG |
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| | ATCATCAAGAAAGGG | GAGTCTCAGAGCACA | ACAGAATATGGTCCC |
| 45 | TCATCAAGAAAGGGC | AGTCTCAGAGCACAG | CAGAATATGGTCCCT |
| | CATCAAGAAAGGGCA | GTCTCAGAGCACAGA | AGAATATGGTCCCTG |
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| | CAAGAAAGGGCATGC | TCAGAGCACAGATAC | ATATGGTCCCTGCCG |
| 50 | AAGAAAGGGCATGCT | CAGAGCACAGATACC | TATGGTCCCTGCCGT |
| | AGAAAGGGCATGCTA | AGAGCACAGATACCC | ATGGTCCCTGCCGTA |

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|---|---|---|---|
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| 15 | GAGAAATGGAAGACA | CCAGGGGTGTACACA | AGCAGTGTCGCCCTT |
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| | GGAAGACACACTGAA | TGTACACATTCCCAA | TCGCCCTTCCAAAGG |
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| | AAGACACACTGAATC | TACACATTCCCAACT | GCCCTTCCAAAGGCA |
| 25 | AGACACACTGAATCA | ACACATTCCCAACTG | CCCTTCCAAAGGCAG |
| | GACACACTGAATCAC | CACATTCCCAACTGT | CCTTCCAAAGGCAGG |
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| | GAATCACCTGAAGTT | CAACTGTGACAAGAA | AGGCAGGAAGCGGGG |
| 35 | AATCACCTGAAGTTC | AACTGTGACAAGAAG | GGCAGGAAGCGGGGC |
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| 50 | CTCAATGTGCTGAGT | GGATTTTATAAGAAA | TTCTGCTGGTGTGTG |
| | TCAATGTGCTGAGTC | GATTTTATAAGAAAA | TCTGCTGGTGTGTGG |

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|---|---|---|---|
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| | CTGGTGTGTGGATAA | GAAGGAGGACGTGCA | AAGTTAATGTGGAGC |
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| | GGTGTGTGGATAAGT | AGGAGGACGTGCACT | GTTAATGTGGAGCTC |
| | GTGTGTGGATAAGTA | GGAGGACGTGCACTG | TTAATGTGGAGCTCA |
| | TGTGTGGATAAGTAT | GAGGACGTGCACTGC | TAATGTGGAGCTCAA |
| | GTGTGGATAAGTATG | AGGACGTGCACTGCT | AATGTGGAGCTCAAA |
| 10 | TGTGGATAAGTATGG | GGACGTGCACTGCTA | ATGTGGAGCTCAAAT |
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| | TGGATAAGTATGGGC | ACGTGCACTGCTACA | GTGGAGCTCAAATAT |
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| 15 | ATAAGTATGGGCAGC | TGCACTGCTACAGCA | GAGCTCAAATATGCC |
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| 20 | TATGGGCAGCCTCTC | TGCTACAGCATGCAG | CAAATATGCCTTATT |
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| 25 | GCAGCCTCTCCCAGG | CAGCATGCAGAGCAA | ATGCCTTATTTTGCA |
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| | AGCCTCTCCCAGGCT | GCATGCAGAGCAAGT | GCCTTATTTTGCACA |
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| | TCCCAGGCTACACCA | AGAGCAAGTAGACGC | TTTTGCACAAAAGAC |
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| 35 | CCAGGCTACACCACC | AGCAAGTAGACGCCT | TTGCACAAAAGACTG |
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| | GCTACACCACCAAGG | AGTAGACGCCTGCCG | ACAAAAGACTGCCAA |
| 40 | CTACACCACCAAGGG | GTAGACGCCTGCCGC | CAAAAGACTGCCAAG |
| | TACACCACCAAGGGG | TAGACGCCTGCCGCA | AAAAGACTGCCAAGG |
| | ACACCACCAAGGGGA | AGACGCCTGCCGCAA | AAAGACTGCCAAGGA |
| | CACCACCAAGGGGAA | GACGCCTGCCGCAAG | AAGACTGCCAAGGAC |
| | ACCACCAAGGGGAAG | ACGCCTGCCGCAAGT | AGACTGCCAAGGACA |
| 45 | CCACCAAGGGGAAGG | CGCCTGCCGCAAGTT | GACTGCCAAGGACAT |
| | CACCAAGGGGAAGGA | GCCTGCCGCAAGTTA | ACTGCCAAGGACATG |
| | ACCAAGGGGAAGGAG | CCTGCCGCAAGTTAA | CTGCCAAGGACATGA |
| | CCAAGGGGAAGGAGG | CTGCCGCAAGTTAAT | TGCCAAGGACATGAC |
| | CAAGGGGAAGGAGGA | TGCCGCAAGTTAATG | GCCAAGGACATGACC |
| 50 | AAGGGGAAGGAGGAC | GCCGCAAGTTAATGT | CCAAGGACATGACCA |
| | AGGGGAAGGAGGACG | CCGCAAGTTAATGTG | CAAGGACATGACCAG |

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|---|---|---|---|
| | AAGGACATGACCAGC | GTGAACTGATTTTTT | TATGGTTTCTTTGAA |
| | AGGACATGACCAGCA | TGAACTGATTTTTTT | ATGGTTTCTTTGAAT |
| | GGACATGACCAGCAG | GAACTGATTTTTTTT | TGGTTTCTTTGAATG |
| | GACATGACCAGCAGC | AACTGATTTTTTTTA | GGTTTCTTTGAATGG |
| 5 | ACATGACCAGCAGCT | ACTGATTTTTTTTAA | GTTTCTTTGAATGGT |
| | CATGACCAGCAGCTG | CTGATTTTTTTTAAA | TTTCTTTGAATGGTA |
| | ATGACCAGCAGCTGG | TGATTTTTTTTAAAC | TTCTTTGAATGGTAA |
| | TGACCAGCAGCTGGC | GATTTTTTTTAAACC | TCTTTGAATGGTAAA |
| | GACCAGCAGCTGGCT | ATTTTTTTTAAACCA | CTTTGAATGGTAAAC |
| 10 | ACCAGCAGCTGGCTA | TTTTTTTTAAACCAA | TTTGAATGGTAAACT |
| | CCAGCAGCTGGCTAC | TTTTTTTAAACCAAA | TTGAATGGTAAACTT |
| | CAGCAGCTGGCTACA | TTTTTTAAACCAAAG | TGAATGGTAAACTTG |
| | AGCAGCTGGCTACAG | TTTTTAAACCAAAGT | GAATGGTAAACTTGA |
| | GCAGCTGGCTACAGC | TTTTAAACCAAAGTT | AATGGTAAACTTGAG |
| 15 | CAGCTGGCTACAGCC | TTTAAACCAAAGTTT | ATGGTAAACTTGAGC |
| | AGCTGGCTACAGCCT | TTAAACCAAAGTTTA | TGGTAAACTTGAGCA |
| | GCTGGCTACAGCCTC | TAAACCAAAGTTTAG | GGTAAACTTGAGCAT |
| | CTGGCTACAGCCTCG | AAACCAAAGTTTAGA | GTAAACTTGAGCATC |
| | TGGCTACAGCCTCGA | AACCAAAGTTTAGAA | TAAACTTGAGCATCT |
| 20 | GGCTACAGCCTCGAT | ACCAAAGTTTAGAAA | AAACTTGAGCATCTT |
| | GCTACAGCCTCGATT | CCAAAGTTTAGAAAG | AACTTGAGCATCTTT |
| | CTACAGCCTCGATTT | CAAAGTTTAGAAAGA | ACTTGAGCATCTTTT |
| | TACAGCCTCGATTTA | AAAGTTTAGAAAGAG | CTTGAGCATCTTTTC |
| | ACAGCCTCGATTTAT | AAGTTTAGAAAGAGG | TTGAGCATCTTTTCA |
| 25 | CAGCCTCGATTTATA | AGTTTAGAAAGAGGT | TGAGCATCTTTTCAC |
| | AGCCTCGATTTATAT | GTTTAGAAAGAGGTT | GAGCATCTTTTCACT |
| | GCCTCGATTTATATT | TTTAGAAAGAGGTTT | AGCATCTTTTCACTT |
| | CCTCGATTTATATTT | TTAGAAAGAGGTTTT | GCATCTTTTCACTTT |
| | CTCGATTTATATTTC | TAGAAAGAGGTTTTT | CATCTTTTCACTTTC |
| 30 | TCGATTTATATTTCT | AGAAAGAGGTTTTTG | ATCTTTTCACTTTCC |
| | CGATTTATATTTCTG | GAAAGAGGTTTTTGA | TCTTTTCACTTTCCA |
| | GATTTATATTTCTGT | AAAGAGGTTTTTGAA | CTTTTCACTTTCCAG |
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| | TTTATATTTCTGTTT | AGAGGTTTTTGAAAT | TTTCACTTTCCAGTA |
| 35 | TTATATTTCTGTTTG | GAGGTTTTTGAAATG | TTCACTTTCCAGTAG |
| | TATATTTCTGTTTGT | AGGTTTTTGAAATGC | TCACTTTCCAGTAGT |
| | ATATTTCTGTTTGTG | GGTTTTTGAAATGCC | CACTTTCCAGTAGTC |
| | TATTTCTGTTTGTGG | GTTTTTGAAATGCCT | ACTTTCCAGTAGTCA |
| | ATTTCTGTTTGTGGT | TTTTTGAAATGCCTA | CTTTCCAGTAGTCAG |
| 40 | TTTCTGTTTGTGGTG | TTTTGAAATGCCTAT | TTTCCAGTAGTCAGC |
| | TTCTGTTTGTGGTGA | TTTGAAATGCCTATG | TTCCAGTAGTCAGCA |
| | TCTGTTTGTGGTGAA | TTGAAATGCCTATGG | TCCAGTAGTCAGCAA |
| | CTGTTTGTGGTGAAC | TGAAATGCCTATGGT | CCAGTAGTCAGCAAA |
| | TGTTTGTGGTGAACT | GAAATGCCTATGGTT | CAGTAGTCAGCAAAG |
| 45 | GTTTGTGGTGAACTG | AAATGCCTATGGTTT | AGTAGTCAGCAAAGA |
| | TTTGTGGTGAACTGA | AATGCCTATGGTTTC | GTAGTCAGCAAAGAG |
| | TTGTGGTGAACTGAT | ATGCCTATGGTTTCT | TAGTCAGCAAAGAGC |
| | TGTGGTGAACTGATT | TGCCTATGGTTTCTT | AGTCAGCAAAGAGCA |
| | GTGGTGAACTGATTT | GCCTATGGTTTCTTT | GTCAGCAAAGAGCAG |
| 50 | TGGTGAACTGATTTT | CCTATGGTTTCTTTG | TCAGCAAAGAGCAGT |
| | GGTGAACTGATTTTT | CTATGGTTTCTTTGA | CAGCAAAGAGCAGTT |

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|---|---|---|---|
| | AGCAAAGAGCAGTTT | ACTCGAGCACAGCAC | TTGGTCGAAGCGGCC |
| | GCAAAGAGCAGTTTG | CTCGAGCACAGCACC | TGGTCGAAGCGGCCG |
| | CAAAGAGCAGTTTGA | TCGAGCACAGCACCC | GGTCGAAGCGGCCGA |
| | AAAGAGCAGTTTGAA | CGAGCACAGCACCCA | GTCGAAGCGGCCGAC |
| 5 | AAGAGCAGTTTGAAT | GAGCACAGCACCCAG | TCGAAGCGGCCGACC |
| | AGAGCAGTTTGAATT | AGCACAGCACCCAGA | CGAAGCGGCCGACCA |
| | GAGCAGTTTGAATTT | GCACAGCACCCAGAC | GAAGCGGCCGACCAC |
| | AGCAGTTTGAATTTT | CACAGCACCCAGACT | AAGCGGCCGACCACT |
| | GCAGTTTGAATTTTC | ACAGCACCCAGACTT | AGCGGCCGACCACTG |
| 10 | CAGTTTGAATTTTCT | CAGCACCCAGACTTC | GCGGCCGACCACTGA |
| | AGTTTGAATTTTCTT | AGCACCCAGACTTCA | CGGCCGACCACTGAC |
| | GTTTGAATTTTCTTG | GCACCCAGACTTCAT | GGCCGACCACTGACT |
| | TTTGAATTTTCTTGT | CACCCAGACTTCATG | GCCGACCACTGACTT |
| | TTGAATTTTCTTGTC | ACCCAGACTTCATGC | CCGACCACTGACTTT |
| 15 | TGAATTTTCTTGTCG | CCCAGACTTCATGCG | CGACCACTGACTTTG |
| | GAATTTTCTTGTCGC | CCAGACTTCATGCGC | GACCACTGACTTTGT |
| | AATTTTCTTGTCGCT | CAGACTTCATGCGCC | ACCACTGACTTTGTG |
| | ATTTTCTTGTCGCTT | AGACTTCATGCGCCC | CCACTGACTTTGTGA |
| | TTTTCTTGTCGCTTC | GACTTCATGCGCCCG | CACTGACTTTGTGAC |
| 20 | TTTCTTGTCGCTTCC | ACTTCATGCGCCCGT | ACTGACTTTGTGACT |
| | TTCTTGTCGCTTCCT | CTTCATGCGCCCGTG | CTGACTTTGTGACTT |
| | TCTTGTCGCTTCCTA | TTCATGCGCCCGTGG | TGACTTTGTGACTTA |
| | CTTGTCGCTTCCTAT | TCATGCGCCCGTGGA | GACTTTGTGACTTAG |
| | TTGTCGCTTCCTATC | CATGCGCCCGTGGAA | ACTTTGTGACTTAGG |
| 25 | TGTCGCTTCCTATCA | ATGCGCCCGTGGAAT | CTTTGTGACTTAGGC |
| | GTCGCTTCCTATCAA | TGCGCCCGTGGAATG | TTTGTGACTTAGGCG |
| | TCGCTTCCTATCAAA | GCGCCCGTGGAATGC | TTGTGACTTAGGCGG |
| | CGCTTCCTATCAAAA | CGCCCGTGGAATGCT | TGTGACTTAGGCGGC |
| | GCTTCCTATCAAAAT | GCCCGTGGAATGCTC | GTGACTTAGGCGGCT |
| 30 | CTTCCTATCAAAATA | CCCGTGGAATGCTCA | TGACTTAGGCGGCTG |
| | TTCCTATCAAAATAT | CCGTGGAATGCTCAC | GACTTAGGCGGCTGT |
| | TCCTATCAAAATATT | CGTGGAATGCTCACC | ACTTAGGCGGCTGTG |
| | CCTATCAAAATATTC | GTGGAATGCTCACCA | CTTAGGCGGCTGTGT |
| | CTATCAAAATATTCA | TGGAATGCTCACCAC | TTAGGCGGCTGTGTT |
| 35 | TATCAAAATATTCAG | GGAATGCTCACCACA | TAGGCGGCTGTGTTG |
| | ATCAAAATATTCAGA | GAATGCTCACCACAT | AGGCGGCTGTGTTGC |
| | TCAAAATATTCAGAG | AATGCTCACCACATG | GGCGGCTGTGTTGCC |
| | CAAAATATTCAGAGA | ATGCTCACCACATGT | GCGGCTGTGTTGCCT |
| | AAAATATTCAGAGAC | TGCTCACCACATGTT | CGGCTGTGTTGCCTA |
| 40 | AAATATTCAGAGACT | GCTCACCACATGTTG | GGCTGTGTTGCCTAT |
| | AATATTCAGAGACTC | CTCACCACATGTTGG | GCTGTGTTGCCTATG |
| | ATATTCAGAGACTCG | TCACCACATGTTGGT | CTGTGTTGCCTATGT |
| | TATTCAGAGACTCGA | CACCACATGTTGGTC | TGTGTTGCCTATGTA |
| | ATTCAGAGACTCGAG | ACCACATGTTGGTCG | GTGTTGCCTATGTAG |
| 45 | TTCAGAGACTCGAGC | CCACATGTTGGTCGA | TGTTGCCTATGTAGA |
| | TCAGAGACTCGAGCA | CACATGTTGGTCGAA | GTTGCCTATGTAGAG |
| | CAGAGACTCGAGCAC | ACATGTTGGTCGAAG | TTGCCTATGTAGAGA |
| | AGAGACTCGAGCACA | CATGTTGGTCGAAGC | TGCCTATGTAGAGAA |
| | GAGACTCGAGCACAG | ATGTTGGTCGAAGCG | GCCTATGTAGAGAAC |
| 50 | AGACTCGAGCACAGC | TGTTGGTCGAAGCGG | CCTATGTAGAGAACA |
| | GACTCGAGCACAGCA | GTTGGTCGAAGCGGC | CTATGTAGAGAACAC |

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|---|---|---|---|
| | TATGTAGAGAACACG | TATCGAGAATAGGAA | ATGCTCCTGGAGCTC |
| | ATGTAGAGAACACGC | ATCGAGAATAGGAAA | TGCTCCTGGAGCTCA |
| | TGTAGAGAACACGCT | TCGAGAATAGGAAAA | GCTCCTGGAGCTCAC |
| | GTAGAGAACACGCTT | CGAGAATAGGAAAAC | CTCCTGGAGCTCACA |
| 5 | TAGAGAACACGCTTC | GAGAATAGGAAAACC | TCCTGGAGCTCACAG |
| | AGAGAACACGCTTCA | AGAATAGGAAAACCT | CCTGGAGCTCACAGC |
| | GAGAACACGCTTCAC | GAATAGGAAAACCTT | CTGGAGCTCACAGCC |
| | AGAACACGCTTCACC | AATAGGAAAACCTTT | TGGAGCTCACAGCCT |
| | GAACACGCTTCACCC | ATAGGAAAACCTTTA | GGAGCTCACAGCCTT |
| 10 | AACACGCTTCACCCC | TAGGAAAACCTTTAA | GAGCTCACAGCCTTC |
| | ACACGCTTCACCCCC | AGGAAAACCTTTAAA | AGCTCACAGCCTTCT |
| | CACGCTTCACCCCCA | GGAAAACCTTTAAAC | GCTCACAGCCTTCTG |
| | ACGCTTCACCCCCAC | GAAAACCTTTAAACC | CTCACAGCCTTCTGT |
| | CGCTTCACCCCCACT | AAAACCTTTAAACCC | TCACAGCCTTCTGTG |
| 15 | GCTTCACCCCCACTC | AAACCTTTAAACCCC | CACAGCCTTCTGTGG |
| | CTTCACCCCCACTCC | AACCTTTAAACCCCG | ACAGCCTTCTGTGGT |
| | TTCACCCCCACTCCC | ACCTTTAAACCCCGG | CAGCCTTCTGTGGTG |
| | TCACCCCCACTCCCC | CCTTTAAACCCCGGT | AGCCTTCTGTGGTGT |
| | CACCCCCACTCCCCG | CTTTAAACCCCGGTC | GCCTTCTGTGGTGTC |
| 20 | ACCCCCACTCCCCGT | TTTAAACCCCGGTCA | CCTTCTGTGGTGTCA |
| | CCCCCACTCCCCGTA | TTAAACCCCGGTCAT | CTTCTGTGGTGTCAT |
| | CCCCACTCCCCGTAC | TAAACCCCGGTCATC | TTCTGTGGTGTCATT |
| | CCCACTCCCCGTACA | AAACCCCGGTCATCC | TCTGTGGTGTCATTT |
| | CCACTCCCCGTACAG | AACCCCGGTCATCCG | CTGTGGTGTCATTTC |
| 25 | CACTCCCCGTACAGT | ACCCCGGTCATCCGG | TGTGGTGTCATTTCT |
| | ACTCCCCGTACAGTG | CCCCGGTCATCCGGA | GTGGTGTCATTTCTG |
| | CTCCCCGTACAGTGC | CCCGGTCATCCGGAC | TGGTGTCATTTCTGA |
| | TCCCCGTACAGTGCG | CCGGTCATCCGGACA | GGTGTCATTTCTGAA |
| | CCCCGTACAGTGCGC | CGGTCATCCGGACAT | GTGTCATTTCTGAAA |
| 30 | CCCGTACAGTGCGCA | GGTCATCCGGACATC | TGTCATTTCTGAAAC |
| | CCGTACAGTGCGCAC | GTCATCCGGACATCC | GTCATTTCTGAAACA |
| | CGTACAGTGCGCACA | TCATCCGGACATCCC | TCATTTCTGAAACAA |
| | GTACAGTGCGCACAG | CATCCGGACATCCCA | CATTTCTGAAACAAG |
| | TACAGTGCGCACAGG | ATCCGGACATCCCAA | ATTTCTGAAACAAGG |
| 35 | ACAGTGCGCACAGGC | TCCGGACATCCCAAC | TTTCTGAAACAAGGG |
| | CAGTGCGCACAGGCT | CCGGACATCCCAACG | TTCTGAAACAAGGGC |
| | AGTGCGCACAGGCTT | CGGACATCCCAACGC | TCTGAAACAAGGGCG |
| | GTGCGCACAGGCTTT | GGACATCCCAACGCA | CTGAAACAAGGGCGT |
| | TGCGCACAGGCTTTA | GACATCCCAACGCAT | TGAAACAAGGGCGTG |
| 40 | GCGCACAGGCTTTAT | ACATCCCAACGCATG | GAAACAAGGGCGTGG |
| | CGCACAGGCTTTATC | CATCCCAACGCATGC | AAACAAGGGCGTGGA |
| | GCACAGGCTTTATCG | ATCCCAACGCATGCT | AACAAGGGCGTGGAT |
| | CACAGGCTTTATCGA | TCCCAACGCATGCTC | ACAAGGGCGTGGATC |
| | ACAGGCTTTATCGAG | CCCAACGCATGCTCC | CAAGGGCGTGGATCC |
| 45 | CAGGCTTTATCGAGA | CCAACGCATGCTCCT | AAGGGCGTGGATCCC |
| | AGGCTTTATCGAGAA | CAACGCATGCTCCTG | AGGGCGTGGATCCCT |
| | GGCTTTATCGAGAAT | AACGCATGCTCCTGG | GGGCGTGGATCCCTC |
| | GCTTTATCGAGAATA | ACGCATGCTCCTGGA | GGCGTGGATCCCTCA |
| | CTTTATCGAGAATAG | CGCATGCTCCTGGAG | GCGTGGATCCCTCAA |
| 50 | TTTATCGAGAATAGG | GCATGCTCCTGGAGC | CGTGGATCCCTCAAC |
| | TTATCGAGAATAGGA | CATGCTCCTGGAGCT | GTGGATCCCTCAACC |

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|---|---|---|---|
| | TGGATCCCTCAACCA | TTGGGGACTATTGGA | GTATCTAAGAATGTT |
| | GGATCCCTCAACCAA | TGGGGACTATTGGAG | TATCTAAGAATGTTC |
| | GATCCCTCAACCAAG | GGGGACTATTGGAGA | ATCTAAGAATGTTCT |
| | ATCCCTCAACCAAGA | GGGACTATTGGAGAA | TCTAAGAATGTTCTA |
| 5 | TCCCTCAACCAAGAA | GGACTATTGGAGAAA | CTAAGAATGTTCTAG |
| | CCCTCAACCAAGAAG | GACTATTGGAGAAAA | TAAGAATGTTCTAGG |
| | CCTCAACCAAGAAGA | ACTATTGGAGAAAAT | AAGAATGTTCTAGGG |
| | CTCAACCAAGAAGAA | CTATTGGAGAAAATA | AGAATGTTCTAGGGC |
| | TCAACCAAGAAGAAT | TATTGGAGAAAATAA | GAATGTTCTAGGGCA |
| 10 | CAACCAAGAAGAATG | ATTGGAGAAAATAAG | AATGTTCTAGGGCAC |
| | AACCAAGAAGAATGT | TTGGAGAAAATAAGG | ATGTTCTAGGGCACT |
| | ACCAAGAAGAATGTT | TGGAGAAAATAAGGT | TGTTCTAGGGCACTC |
| | CCAAGAAGAATGTTT | GGAGAAAATAAGGTG | GTTCTAGGGCACTCT |
| | CAAGAAGAATGTTTA | GAGAAAATAAGGTGG | TTCTAGGGCACTCTG |
| 15 | AAGAAGAATGTTTAT | AGAAAATAAGGTGGA | TCTAGGGCACTCTGG |
| | AGAAGAATGTTTATG | GAAAATAAGGTGGAG | CTAGGGCACTCTGGG |
| | GAAGAATGTTTATGT | AAAATAAGGTGGAGT | TAGGGCACTCTGGGA |
| | AAGAATGTTTATGTC | AAATAAGGTGGAGTC | AGGGCACTCTGGGAA |
| | AGAATGTTTATGTCT | AATAAGGTGGAGTCC | GGGCACTCTGGGAAC |
| 20 | GAATGTTTATGTCTT | ATAAGGTGGAGTCCT | GGCACTCTGGGAACC |
| | AATGTTTATGTCTTC | TAAGGTGGAGTCCTA | GCACTCTGGGAACCT |
| | ATGTTTATGTCTTCA | AAGGTGGAGTCCTAC | CACTCTGGGAACCTA |
| | TGTTTATGTCTTCAA | AGGTGGAGTCCTACT | ACTCTGGGAACCTAT |
| | GTTTATGTCTTCAAG | GGTGGAGTCCTACTT | CTCTGGGAACCTATA |
| 25 | TTTATGTCTTCAAGT | GTGGAGTCCTACTTG | TCTGGGAACCTATAA |
| | TTATGTCTTCAAGTG | TGGAGTCCTACTTGT | CTGGGAACCTATAAA |
| | TATGTCTTCAAGTGA | GGAGTCCTACTTGTT | TGGGAACCTATAAAG |
| | ATGTCTTCAAGTGAC | GAGTCCTACTTGTTT | GGGAACCTATAAAGG |
| | TGTCTTCAAGTGACC | AGTCCTACTTGTTTA | GGAACCTATAAAGGC |
| 30 | GTCTTCAAGTGACCT | GTCCTACTTGTTTAA | GAACCTATAAAGGCA |
| | TCTTCAAGTGACCTG | TCCTACTTGTTTAAA | AACCTATAAAGGCAG |
| | CTTCAAGTGACCTGT | CCTACTTGTTTAAAA | ACCTATAAAGGCAGG |
| | TTCAAGTGACCTGTA | CTACTTGTTTAAAAA | CCTATAAAGGCAGGT |
| | TCAAGTGACCTGTAC | TACTTGTTTAAAAAA | CTATAAAGGCAGGTA |
| 35 | CAAGTGACCTGTACT | ACTTGTTTAAAAAAT | TATAAAGGCAGGTAT |
| | AAGTGACCTGTACTG | CTTGTTTAAAAAATA | ATAAAGGCAGGTATT |
| | AGTGACCTGTACTGC | TTGTTTAAAAAATAT | TAAAGGCAGGTATTT |
| | GTGACCTGTACTGCT | TGTTTAAAAAATATG | AAAGGCAGGTATTTC |
| | TGACCTGTACTGCTT | GTTTAAAAAATATGT | AAGGCAGGTATTTCG |
| 40 | GACCTGTACTGCTTG | TTTAAAAAATATGTA | AGGCAGGTATTTCGG |
| | ACCTGTACTGCTTGG | TTAAAAAATATGTAT | GGCAGGTATTTCGGG |
| | CCTGTACTGCTTGGG | TAAAAAATATGTATC | GCAGGTATTTCGGGC |
| | CTGTACTGCTTGGGG | AAAAAATATGTATCT | CAGGTATTTCGGGCC |
| | TGTACTGCTTGGGGA | AAAAATATGTATCTA | AGGTATTTCGGGCCC |
| 45 | GTACTGCTTGGGGAC | AAAATATGTATCTAA | GGTATTTCGGGCCCT |
| | TACTGCTTGGGGACT | AAATATGTATCTAAG | GTATTTCGGGCCCTC |
| | ACTGCTTGGGGACTA | AATATGTATCTAAGA | TATTTCGGGCCCTCC |
| | CTGCTTGGGGACTAT | ATATGTATCTAAGAA | ATTTCGGGCCCTCCT |
| | TGCTTGGGGACTATT | TATGTATCTAAGAAT | TTTCGGGCCCTCCTC |
| 50 | GCTTGGGGACTATTG | ATGTATCTAAGAATG | TTCGGGCCCTCCTCT |
| | CTTGGGGACTATTGG | TGTATCTAAGAATGT | TCGGGCCCTCCTCTT |

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|---|---|---|
| CGGGCCCTCCTCTTC | CAGGATGGCTTTTGC | AGAGTCAGCCTCCAC |
| GGGCCCTCCTCTTCA | AGGATGGCTTTTGCT | GAGTCAGCCTCCACA |
| GGCCCTCCTCTTCAG | GGATGGCTTTTGCTG | AGTCAGCCTCCACAT |
| GCCCTCCTCTTCAGG | GATGGCTTTTGCTGC | GTCAGCCTCCACATT |
| CCCTCCTCTTCAGGA | ATGGCTTTTGCTGCG | TCAGCCTCCACATTC |
| CCTCCTCTTCAGGAA | TGGCTTTTGCTGCGG | CAGCCTCCACATTCA |
| CTCCTCTTCAGGAAT | GGCTTTTGCTGCGGC | AGCCTCCACATTCAG |
| TCCTCTTCAGGAATC | GCTTTTGCTGCGGCC | GCCTCCACATTCAGA |
| CCTCTTCAGGAATCT | CTTTTGCTGCGGCCC | CCTCCACATTCAGAG |
| CTCTTCAGGAATCTT | TTTTGCTGCGGCCCC | CTCCACATTCAGAGG |
| TCTTCAGGAATCTTC | TTTGCTGCGGCCCCG | TCCACATTCAGAGGC |
| CTTCAGGAATCTTCC | TTGCTGCGGCCCCGT | CCACATTCAGAGGCA |
| TTCAGGAATCTTCCT | TGCTGCGGCCCCGTG | CACATTCAGAGGCAT |
| TCAGGAATCTTCCTG | GCTGCGGCCCCGTGG | ACATTCAGAGGCATC |
| CAGGAATCTTCCTGA | CTGCGGCCCCGTGGG | CATTCAGAGGCATCA |
| AGGAATCTTCCTGAA | TGCGGCCCCGTGGGG | ATTCAGAGGCATCAC |
| GGAATCTTCCTGAAG | GCGGCCCCGTGGGGT | TTCAGAGGCATCACA |
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| ATCTTCCTGAAGACA | GCCCCGTGGGGTAGG | AGAGGCATCACAAGT |
| TCTTCCTGAAGACAT | CCCCGTGGGGTAGGA | GAGGCATCACAAGTA |
| CTTCCTGAAGACATG | CCCGTGGGGTAGGAG | AGGCATCACAAGTAA |
| TTCCTGAAGACATGG | CCGTGGGGTAGGAGG | GGCATCACAAGTAAT |
| TCCTGAAGACATGGC | CGTGGGGTAGGAGGG | GCATCACAAGTAATG |
| CCTGAAGACATGGCC | GTGGGGTAGGAGGGA | CATCACAAGTAATGG |
| CTGAAGACATGGCCC | TGGGGTAGGAGGGAC | ATCACAAGTAATGGC |
| TGAAGACATGGCCCA | GGGGTAGGAGGGACA | TCACAAGTAATGGCA |
| GAAGACATGGCCCAG | GGGTAGGAGGGACAG | CACAAGTAATGGCAC |
| AAGACATGGCCCAGT | GGTAGGAGGGACAGA | ACAAGTAATGGCACA |
| AGACATGGCCCAGTC | GTAGGAGGGACAGAG | CAAGTAATGGCACAA |
| GACATGGCCCAGTCG | TAGGAGGGACAGAGA | AAGTAATGGCACAAT |
| ACATGGCCCAGTCGA | AGGAGGGACAGAGAG | AGTAATGGCACAATT |
| CATGGCCCAGTCGAA | GGAGGGACAGAGAGA | GTAATGGCACAATTC |
| ATGGCCCAGTCGAAG | GAGGGACAGAGAGAC | TAATGGCACAATTCT |
| TGGCCCAGTCGAAGG | AGGGACAGAGAGACG | AATGGCACAATTCTT |
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| CCCAGTCGAAGGCCC | GACAGAGAGACGGGA | GGCACAATTCTTCGG |
| CCAGTCGAAGGCCCA | ACAGAGAGACGGGAG | GCACAATTCTTCGGA |
| CAGTCGAAGGCCCAG | CAGAGAGACGGGAGA | CACAATTCTTCGGAT |
| AGTCGAAGGCCCAGG | AGAGAGACGGGAGAG | ACAATTCTTCGGATG |
| GTCGAAGGCCCAGGA | GAGAGACGGGAGAGT | CAATTCTTCGGATGA |
| TCGAAGGCCCAGGAT | AGAGACGGGAGAGTC | AATTCTTCGGATGAC |
| CGAAGGCCCAGGATG | GAGACGGGAGAGTCA | ATTCTTCGGATGACT |
| GAAGGCCCAGGATGG | AGACGGGAGAGTCAG | TTCTTCGGATGACTG |
| AAGGCCCAGGATGGC | GACGGGAGAGTCAGC | TCTTCGGATGACTGC |
| AGGCCCAGGATGGCT | ACGGGAGAGTCAGCC | CTTCGGATGACTGCA |
| GGCCCAGGATGGCTT | CGGGAGAGTCAGCCT | TTCGGATGACTGCAG |
| GCCCAGGATGGCTTT | GGGAGAGTCAGCCTC | TCGGATGACTGCAGA |
| CCCAGGATGGCTTTT | GGAGAGTCAGCCTCC | CGGATGACTGCAGAA |
| CCAGGATGGCTTTTG | GAGAGTCAGCCTCCA | GGATGACTGCAGAAA |

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|---|---|---|---|
| | GATGACTGCAGAAAA | ATTTCTGAGGATAAG | TTTTGTCCTCCTTAG |
| | ATGACTGCAGAAAAT | TTTCTGAGGATAAGC | TTTGTCCTCCTTAGC |
| | TGACTGCAGAAAATA | TTCTGAGGATAAGCT | TTGTCCTCCTTAGCA |
| | GACTGCAGAAAATAG | TCTGAGGATAAGCTC | TGTCCTCCTTAGCAC |
| 5 | ACTGCAGAAAATAGT | CTGAGGATAAGCTCT | GTCCTCCTTAGCACA |
| | CTGCAGAAAATAGTG | TGAGGATAAGCTCTT | TCCTCCTTAGCACAA |
| | TGCAGAAAATAGTGT | GAGGATAAGCTCTTT | CCTCCTTAGCACAAT |
| | GCAGAAAATAGTGTT | AGGATAAGCTCTTTA | CTCCTTAGCACAATG |
| | CAGAAAATAGTGTTT | GGATAAGCTCTTTAA | TCCTTAGCACAATGT |
| 10 | AGAAAATAGTGTTTT | GATAAGCTCTTTAAA | CCTTAGCACAATGTA |
| | GAAAATAGTGTTTTG | ATAAGCTCTTTAAAG | CTTAGCACAATGTAA |
| | AAAATAGTGTTTTGT | TAAGCTCTTTAAAGG | TTAGCACAATGTAAA |
| | AAATAGTGTTTTGTA | AAGCTCTTTAAAGGC | TAGCACAATGTAAAA |
| | AATAGTGTTTTGTAG | AGCTCTTTAAAGGCA | AGCACAATGTAAAAA |
| 15 | ATAGTGTTTTGTAGT | GCTCTTTAAAGGCAA | GCACAATGTAAAAAA |
| | TAGTGTTTTGTAGTT | CTCTTTAAAGGCAAA | CACAATGTAAAAAAG |
| | AGTGTTTTGTAGTTC | TCTTTAAAGGCAAAG | ACAATGTAAAAAAGA |
| | GTGTTTTGTAGTTCA | CTTTAAAGGCAAAGC | CAATGTAAAAAAGAA |
| | TGTTTTGTAGTTCAA | TTTAAAGGCAAAGCT | AATGTAAAAAAGAAT |
| 20 | GTTTTGTAGTTCAAC | TTAAAGGCAAAGCTT | ATGTAAAAAAGAATA |
| | TTTTGTAGTTCAACA | TAAAGGCAAAGCTTT | TGTAAAAAAGAATAG |
| | TTTGTAGTTCAACAA | AAAGGCAAAGCTTTA | GTAAAAAAGAATAGT |
| | TTGTAGTTCAACAAC | AAGGCAAAGCTTTAT | TAAAAAAGAATAGTA |
| | TGTAGTTCAACAACT | AGGCAAAGCTTTATT | AAAAAAGAATAGTAA |
| 25 | GTAGTTCAACAACTC | GGCAAAGCTTTATTT | AAAAAGAATAGTAAT |
| | TAGTTCAACAACTCA | GCAAAGCTTTATTTT | AAAAGAATAGTAATA |
| | AGTTCAACAACTCAA | CAAAGCTTTATTTTC | AAAGAATAGTAATAT |
| | GTTCAACAACTCAAG | AAAGCTTTATTTTCA | AAGAATAGTAATATC |
| | TTCAACAACTCAAGA | AAGCTTTATTTTCAT | AGAATAGTAATATCA |
| 30 | TCAACAACTCAAGAC | AGCTTTATTTTCATC | GAATAGTAATATCAG |
| | CAACAACTCAAGACG | GCTTTATTTTCATCT | AATAGTAATATCAGA |
| | AACAACTCAAGACGA | CTTTATTTTCATCTC | ATAGTAATATCAGAA |
| | ACAACTCAAGACGAA | TTTATTTTCATCTCT | TAGTAATATCAGAAC |
| | CAACTCAAGACGAAG | TTATTTTCATCTCTC | AGTAATATCAGAACA |
| 35 | AACTCAAGACGAAGC | TATTTTCATCTCTCA | GTAATATCAGAACAG |
| | ACTCAAGACGAAGCT | ATTTTCATCTCTCAT | TAATATCAGAACAGG |
| | CTCAAGACGAAGCTT | TTTTCATCTCTCATC | AATATCAGAACAGGA |
| | TCAAGACGAAGCTTA | TTTCATCTCTCATCT | ATATCAGAACAGGAA |
| | CAAGACGAAGCTTAT | TTCATCTCTCATCTT | TATCAGAACAGGAAG |
| 40 | AAGACGAAGCTTATT | TCATCTCTCATCTTT | ATCAGAACAGGAAGG |
| | AGACGAAGCTTATTT | CATCTCTCATCTTTT | TCAGAACAGGAAGGA |
| | GACGAAGCTTATTTC | ATCTCTCATCTTTTG | CAGAACAGGAAGGAG |
| | ACGAAGCTTATTTCT | TCTCTCATCTTTTGT | AGAACAGGAAGGAGG |
| | CGAAGCTTATTTCTG | CTCTCATCTTTTGTC | GAACAGGAAGGAGGA |
| 45 | GAAGCTTATTTCTGA | TCTCATCTTTTGTCC | AACAGGAAGGAGGAA |
| | AAGCTTATTTCTGAG | CTCATCTTTTGTCCT | ACAGGAAGGAGGAAT |
| | AGCTTATTTCTGAGG | TCATCTTTTGTCCTC | CAGGAAGGAGGAATG |
| | GCTTATTTCTGAGGA | CATCTTTTGTCCTCC | AGGAAGGAGGAATGG |
| | CTTATTTCTGAGGAT | ATCTTTTGTCCTCCT | GGAAGGAGGAATGGC |
| 50 | TTATTTCTGAGGATA | TCTTTTGTCCTCCTT | GAAGGAGGAATGGCT |
| | TATTTCTGAGGATAA | CTTTTGTCCTCCTTA | AAGGAGGAATGGCTT |

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|---|---|---|---|
| | AGGAGGAATGGCTTG | GATTCACCCATGTTT | ATTCACACATATATG |
| | GGAGGAATGGCTTGC | ATTCACCCATGTTTG | TTCACACATATATGC |
| | GAGGAATGGCTTGCT | TTCACCCATGTTTGT | TCACACATATATGCA |
| | AGGAATGGCTTGCTG | TCACCCATGTTTGTT | CACACATATATGCAG |
| 5 | GGAATGGCTTGCTGG | CACCCATGTTTGTTG | ACACATATATGCAGA |
| | GAATGGCTTGCTGGG | ACCCATGTTTGTTGA | CACATATATGCAGAG |
| | AATGGCTTGCTGGGG | CCCATGTTTGTTGAA | ACATATATGCAGAGA |
| | ATGGCTTGCTGGGGA | CCATGTTTGTTGAAC | CATATATGCAGAGAA |
| | TGGCTTGCTGGGGAG | CATGTTTGTTGAACT | ATATATGCAGAGAAG |
| 10 | GGCTTGCTGGGGAGC | ATGTTTGTTGAACTT | TATATGCAGAGAAGA |
| | GCTTGCTGGGGAGCC | TGTTTGTTGAACTTA | ATATGCAGAGAAGAT |
| | CTTGCTGGGGAGCCC | GTTTGTTGAACTTAG | TATGCAGAGAAGATA |
| | TTGCTGGGGAGCCCA | TTTGTTGAACTTAGA | ATGCAGAGAAGATAT |
| | TGCTGGGGAGCCCAT | TTGTTGAACTTAGAG | TGCAGAGAAGATATG |
| 15 | GCTGGGGAGCCCATC | TGTTGAACTTAGAGT | GCAGAGAAGATATGT |
| | CTGGGGAGCCCATCC | GTTGAACTTAGAGTC | CAGAGAAGATATGTT |
| | TGGGGAGCCCATCCA | TTGAACTTAGAGTCA | AGAGAAGATATGTTC |
| | GGGGAGCCCATCCAG | TGAACTTAGAGTCAT | GAGAAGATATGTTCT |
| | GGGAGCCCATCCAGG | GAACTTAGAGTCATT | AGAAGATATGTTCTT |
| 20 | GGAGCCCATCCAGGA | AACTTAGAGTCATTC | GAAGATATGTTCTTG |
| | GAGCCCATCCAGGAC | ACTTAGAGTCATTCT | AAGATATGTTCTTGT |
| | AGCCCATCCAGGACA | CTTAGAGTCATTCTC | AGATATGTTCTTGTT |
| | GCCCATCCAGGACAC | TTAGAGTCATTCTCA | GATATGTTCTTGTTA |
| | CCCATCCAGGACACT | TAGAGTCATTCTCAT | ATATGTTCTTGTTAA |
| 25 | CCATCCAGGACACTG | AGAGTCATTCTCATG | TATGTTCTTGTTAAC |
| | CATCCAGGACACTGG | GAGTCATTCTCATGC | ATGTTCTTGTTAACA |
| | ATCCAGGACACTGGG | AGTCATTCTCATGCT | TGTTCTTGTTAACAT |
| | TCCAGGACACTGGGA | GTCATTCTCATGCTT | GTTCTTGTTAACATT |
| | CCAGGACACTGGGAG | TCATTCTCATGCTTT | TTCTTGTTAACATTG |
| 30 | CAGGACACTGGGAGC | CATTCTCATGCTTTT | TCTTGTTAACATTGT |
| | AGGACACTGGGAGCA | ATTCTCATGCTTTTC | CTTGTTAACATTGTA |
| | GGACACTGGGAGCAC | TTCTCATGCTTTTCT | TTGTTAACATTGTAT |
| | GACACTGGGAGCACA | TCTCATGCTTTTCTT | TGTTAACATTGTATA |
| | ACACTGGGAGCACAT | CTCATGCTTTTCTTT | GTTAACATTGTATAC |
| 35 | CACTGGGAGCACATA | TCATGCTTTTCTTTA | TTAACATTGTATACA |
| | ACTGGGAGCACATAG | CATGCTTTTCTTTAT | TAACATTGTATACAA |
| | CTGGGAGCACATAGA | ATGCTTTTCTTTATA | AACATTGTATACAAC |
| | TGGGAGCACATAGAG | TGCTTTTCTTTATAA | ACATTGTATACAACA |
| | GGGAGCACATAGAGA | GCTTTTCTTTATAAT | CATTGTATACAACAT |
| 40 | GGAGCACATAGAGAT | CTTTTCTTTATAATT | ATTGTATACAACATA |
| | GAGCACATAGAGATT | TTTTCTTTATAATTC | TTGTATACAACATAG |
| | AGCACATAGAGATTC | TTTCTTTATAATTCA | TGTATACAACATAGC |
| | GCACATAGAGATTCA | TTCTTTATAATTCAC | GTATACAACATAGCC |
| | CACATAGAGATTCAC | TCTTTATAATTCACA | TATACAACATAGCCC |
| 45 | ACATAGAGATTCACC | CTTTATAATTCACAC | ATACAACATAGCCCC |
| | CATAGAGATTCACCC | TTTATAATTCACACA | TACAACATAGCCCCA |
| | ATAGAGATTCACCCA | TTATAATTCACACAT | ACAACATAGCCCCAA |
| | TAGAGATTCACCCAT | TATAATTCACACATA | CAACATAGCCCCAAA |
| | AGAGATTCACCCATG | ATAATTCACACATAT | AACATAGCCCCAAAT |
| 50 | GAGATTCACCCATGT | TAATTCACACATATA | ACATAGCCCCAAATA |
| | AGATTCACCCATGTT | AATTCACACATATAT | CATAGCCCCAAATAT |

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|---|---|---|---|
| | ATAGCCCCAAATATA | AGAGATGCTATATGA | CCCAGAGACTGGGCT |
| | TAGCCCCAAATATAG | GAGATGCTATATGAT | CCAGAGACTGGGCTG |
| | AGCCCCAAATATAGT | AGATGCTATATGATA | CAGAGACTGGGCTGC |
| | GCCCCAAATATAGTA | GATGCTATATGATAC | AGAGACTGGGCTGCT |
| 5 | CCCCAAATATAGTAA | ATGCTATATGATACA | GAGACTGGGCTGCTC |
| | CCCAAATATAGTAAG | TGCTATATGATACAA | AGACTGGGCTGCTCT |
| | CCAAATATAGTAAGA | GCTATATGATACAAC | GACTGGGCTGCTCTC |
| | CAAATATAGTAAGAT | CTATATGATACAACT | ACTGGGCTGCTCTCC |
| | AAATATAGTAAGATC | TATATGATACAACTG | CTGGGCTGCTCTCCC |
| 10 | AATATAGTAAGATCT | ATATGATACAACTGT | TGGGCTGCTCTCCCG |
| | ATATAGTAAGATCTA | TATGATACAACTGTG | GGGCTGCTCTCCCGG |
| | TATAGTAAGATCTAT | ATGATACAACTGTGG | GGCTGCTCTCCCGGA |
| | ATAGTAAGATCTATA | TGATACAACTGTGGC | GCTGCTCTCCCGGAG |
| | TAGTAAGATCTATAC | GATACAACTGTGGCC | CTGCTCTCCCGGAGG |
| 15 | AGTAAGATCTATACT | ATACAACTGTGGCCA | TGCTCTCCCGGAGGC |
| | GTAAGATCTATACTA | TACAACTGTGGCCAT | GCTCTCCCGGAGGCC |
| | TAAGATCTATACTAG | ACAACTGTGGCCATG | CTCTCCCGGAGGCCA |
| | AAGATCTATACTAGA | CAACTGTGGCCATGA | TCTCCCGGAGGCCAA |
| | AGATCTATACTAGAT | AACTGTGGCCATGAC | CTCCCGGAGGCCAAA |
| 20 | GATCTATACTAGATA | ACTGTGGCCATGACT | TCCCGGAGGCCAAAC |
| | ATCTATACTAGATAA | CTGTGGCCATGACTG | CCCGGAGGCCAAACC |
| | TCTATACTAGATAAT | TGTGGCCATGACTGA | CCGGAGGCCAAACCC |
| | CTATACTAGATAATC | GTGGCCATGACTGAG | CGGAGGCCAAACCCA |
| | TATACTAGATAATCC | TGGCCATGACTGAGG | GGAGGCCAAACCCAA |
| 25 | ATACTAGATAATCCT | GGCCATGACTGAGGA | GAGGCCAAACCCAAG |
| | TACTAGATAATCCTA | GCCATGACTGAGGAA | AGGCCAAACCCAAGA |
| | ACTAGATAATCCTAG | CCATGACTGAGGAAA | GGCCAAACCCAAGAA |
| | CTAGATAATCCTAGA | CATGACTGAGGAAAG | GCCAAACCCAAGAAG |
| | TAGATAATCCTAGAT | ATGACTGAGGAAAGG | CCAAACCCAAGAAGG |
| 30 | AGATAATCCTAGATG | TGACTGAGGAAAGGA | CAAACCCAAGAAGGT |
| | GATAATCCTAGATGA | GACTGAGGAAAGGAG | AAACCCAAGAAGGTC |
| | ATAATCCTAGATGAA | ACTGAGGAAAGGAGC | AACCCAAGAAGGTCT |
| | TAATCCTAGATGAAA | CTGAGGAAAGGAGCT | ACCCAAGAAGGTCTG |
| | AATCCTAGATGAAAT | TGAGGAAAGGAGCTC | CCCAAGAAGGTCTGG |
| 35 | ATCCTAGATGAAATG | GAGGAAAGGAGCTCA | CCAAGAAGGTCTGGC |
| | TCCTAGATGAAATGT | AGGAAAGGAGCTCAC | CAAGAAGGTCTGGCA |
| | CCTAGATGAAATGTT | GGAAAGGAGCTCACG | AAGAAGGTCTGGCAA |
| | CTAGATGAAATGTTA | GAAAGGAGCTCACGC | AGAAGGTCTGGCAAA |
| | TAGATGAAATGTTAG | AAAGGAGCTCACGCC | GAAGGTCTGGCAAAG |
| 40 | AGATGAAATGTTAGA | AAGGAGCTCACGCCC | AAGGTCTGGCAAAGT |
| | GATGAAATGTTAGAG | AGGAGCTCACGCCCA | AGGTCTGGCAAAGTC |
| | ATGAAATGTTAGAGA | GGAGCTCACGCCCAG | GGTCTGGCAAAGTCA |
| | TGAAATGTTAGAGAT | GAGCTCACGCCCAGA | GTCTGGCAAAGTCAG |
| | GAAATGTTAGAGATG | AGCTCACGCCCAGAG | TCTGGCAAAGTCAGG |
| 45 | AAATGTTAGAGATGC | GCTCACGCCCAGAGA | CTGGCAAAGTCAGGC |
| | AATGTTAGAGATGCT | CTCACGCCCAGAGAC | TGGCAAAGTCAGGCT |
| | ATGTTAGAGATGCTA | TCACGCCCAGAGACT | GGCAAAGTCAGGCTC |
| | TGTTAGAGATGCTAT | CACGCCCAGAGACTG | GCAAAGTCAGGCTCA |
| | GTTAGAGATGCTATA | ACGCCCAGAGACTGG | CAAAGTCAGGCTCAG |
| 50 | TTAGAGATGCTATAT | CGCCCAGAGACTGGG | AAAGTCAGGCTCAGG |
| | TAGAGATGCTATATG | GCCCAGAGACTGGGC | AAGTCAGGCTCAGGG |

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|---|---|---|---|
| | AGTCAGGCTCAGGGA | GCTGCATAGAGCTCT | CCTATTAGCTTTTCT |
| | GTCAGGCTCAGGGAG | CTGCATAGAGCTCTC | CTATTAGCTTTTCTT |
| | TCAGGCTCAGGGAGA | TGCATAGAGCTCTCC | TATTAGCTTTTCTTT |
| | CAGGCTCAGGGAGAC | GCATAGAGCTCTCCT | ATTAGCTTTTCTTTA |
| 5 | AGGCTCAGGGAGACT | CATAGAGCTCTCCTT | TTAGCTTTTCTTTAT |
| | GGCTCAGGGAGACTC | ATAGAGCTCTCCTTG | TAGCTTTTCTTTATT |
| | GCTCAGGGAGACTCT | TAGAGCTCTCCTTGA | AGCTTTTCTTTATTT |
| | CTCAGGGAGACTCTG | AGAGCTCTCCTTGAA | GCTTTTCTTTATTTT |
| | TCAGGGAGACTCTGC | GAGCTCTCCTTGAAA | CTTTTCTTTATTTTT |
| 10 | CAGGGAGACTCTGCC | AGCTCTCCTTGAAAA | TTTTCTTTATTTTTT |
| | AGGGAGACTCTGCCC | GCTCTCCTTGAAAAC | TTTCTTTATTTTTTT |
| | GGGAGACTCTGCCCT | CTCTCCTTGAAAACA | TTCTTTATTTTTTTA |
| | GGAGACTCTGCCCTG | TCTCCTTGAAAACAG | TCTTTATTTTTTTAA |
| | GAGACTCTGCCCTGC | CTCCTTGAAAACAGA | CTTTATTTTTTTAAC |
| 15 | AGACTCTGCCCTGCT | TCCTTGAAAACAGAG | TTTATTTTTTTAACT |
| | GACTCTGCCCTGCTG | CCTTGAAAACAGAGG | TTATTTTTTTAACTT |
| | ACTCTGCCCTGCTGC | CTTGAAAACAGAGGG | TATTTTTTTAACTTT |
| | CTCTGCCCTGCTGCA | TTGAAAACAGAGGGG | ATTTTTTTAACTTTT |
| | TCTGCCCTGCTGCAG | TGAAAACAGAGGGGT | TTTTTTTAACTTTTT |
| 20 | CTGCCCTGCTGCAGA | GAAAACAGAGGGGTC | TTTTTTAACTTTTTG |
| | TGCCCTGCTGCAGAC | AAAACAGAGGGGTCT | TTTTTAACTTTTTGG |
| | GCCCTGCTGCAGACC | AAACAGAGGGGTCTC | TTTTAACTTTTTGGG |
| | CCCTGCTGCAGACCT | AACAGAGGGGTCTCA | TTTAACTTTTTGGGG |
| | CCTGCTGCAGACCTC | ACAGAGGGGTCTCAA | TTAACTTTTTGGGGG |
| 25 | CTGCTGCAGACCTCG | CAGAGGGGTCTCAAG | TAACTTTTTGGGGGG |
| | TGCTGCAGACCTCGG | AGAGGGGTCTCAAGA | AACTTTTTGGGGGGA |
| | GCTGCAGACCTCGGT | GAGGGGTCTCAAGAC | ACTTTTTGGGGGGAA |
| | CTGCAGACCTCGGTG | AGGGGTCTCAAGACA | CTTTTTGGGGGGAAA |
| | TGCAGACCTCGGTGT | GGGGTCTCAAGACAT | TTTTTGGGGGGAAAA |
| 30 | GCAGACCTCGGTGTG | GGGTCTCAAGACATT | TTTTGGGGGGAAAAG |
| | CAGACCTCGGTGTGG | GGTCTCAAGACATTC | TTTGGGGGGAAAAGT |
| | AGACCTCGGTGTGGA | GTCTCAAGACATTCT | TTGGGGGGAAAAGTA |
| | GACCTCGGTGTGGAC | TCTCAAGACATTCTG | TGGGGGGAAAAGTAT |
| | ACCTCGGTGTGGACA | CTCAAGACATTCTGC | GGGGGGAAAAGTATT |
| 35 | CCTCGGTGTGGACAC | TCAAGACATTCTGCC | GGGGGAAAAGTATTT |
| | CTCGGTGTGGACACA | CAAGACATTCTGCCT | GGGGAAAAGTATTTT |
| | TCGGTGTGGACACAC | AAGACATTCTGCCTA | GGGAAAAGTATTTTT |
| | CGGTGTGGACACACG | AGACATTCTGCCTAC | GGAAAAGTATTTTTG |
| | GGTGTGGACACACGC | GACATTCTGCCTACC | GAAAAGTATTTTTGA |
| 40 | GTGTGGACACACGCT | ACATTCTGCCTACCT | AAAAGTATTTTTGAG |
| | TGTGGACACACGCTG | CATTCTGCCTACCTA | AAAGTATTTTTGAGA |
| | GTGGACACACGCTGC | ATTCTGCCTACCTAT | AAGTATTTTTGAGAA |
| | TGGACACACGCTGCA | TTCTGCCTACCTATT | AGTATTTTTGAGAAG |
| | GGACACACGCTGCAT | TCTGCCTACCTATTA | GTATTTTTGAGAAGT |
| 45 | GACACACGCTGCATA | CTGCCTACCTATTAG | TATTTTTGAGAAGTT |
| | ACACACGCTGCATAG | TGCCTACCTATTAGC | ATTTTTGAGAAGTTT |
| | CACACGCTGCATAGA | GCCTACCTATTAGCT | TTTTTGAGAAGTTTG |
| | ACACGCTGCATAGAG | CCTACCTATTAGCTT | TTTTGAGAAGTTTGT |
| | CACGCTGCATAGAGC | CTACCTATTAGCTTT | TTTGAGAAGTTTGTC |
| 50 | ACGCTGCATAGAGCT | TACCTATTAGCTTTT | TTGAGAAGTTTGTCT |
| | CGCTGCATAGAGCTC | ACCTATTAGCTTTTC | TGAGAAGTTTGTCTT |

GAGAAGTTTGTCTTG
AGAAGTTTGTCTTGC
GAAGTTTGTCTTGCA
AAGTTTGTCTTGCAA
AGTTTGTCTTGCAAT
GTTTGTCTTGCAATG
TTTGTCTTGCAATGT
TTGTCTTGCAATGTA
TGTCTTGCAATGTAT
GTCTTGCAATGTATT
TCTTGCAATGTATTT
CTTGCAATGTATTTA
TTGCAATGTATTTAT
TGCAATGTATTTATA
GCAATGTATTTATAA
CAATGTATTTATAAA
AATGTATTTATAAAT
ATGTATTTATAAATA
TGTATTTATAAATAG
GTATTTATAAATAGT
TATTTATAAATAGTA
ATTTATAAATAGTAA
TTTATAAATAGTAAA
TTATAAATAGTAAAT
TATAAATAGTAAATA
ATAAATAGTAAATAA
TAAATAGTAAATAAA
AAATAGTAAATAAAG
AATAGTAAATAAAGT
ATAGTAAATAAAGTT
TAGTAAATAAAGTTT
AGTAAATAAAGTTTT
GTAAATAAAGTTTTT
TAAATAAAGTTTTTA
AAATAAAGTTTTTAC
AATAAAGTTTTTACC
ATAAAGTTTTTACCA
TAAAGTTTTTACCAT
AAAGTTTTTACCATT

## EXAMPLE 8

Antisense oligonucleotides to IGF-I may be selected from molecules capable of interacting with one or more of the following sense oligonucleotides:

| | | |
|---|---|---|
| TTTTTTTTTTTTTTG | TTTTTTTTTTTGAGA | TTTTTTTTGAGAAAG |
| TTTTTTTTTTTTTGA | TTTTTTTTTTGAGAA | TTTTTTTGAGAAAGG |
| TTTTTTTTTTTTGAG | TTTTTTTTTGAGAAA | TTTTTTGAGAAAGGG |

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|---|---|---|---|
| | TTTTTGAGAAAGGGA | GGAGGAGGGTCCCCG | CTCTCGCTCTGGCCG |
| | TTTTGAGAAAGGGAA | GAGGAGGGTCCCCGA | TCTCGCTCTGGCCGA |
| | TTTGAGAAAGGGAAT | AGGAGGGTCCCCGAC | CTCGCTCTGGCCGAC |
| | TTGAGAAAGGGAATT | GGAGGGTCCCCGACC | TCGCTCTGGCCGACG |
| 5 | TGAGAAAGGGAATTT | GAGGGTCCCCGACCT | CGCTCTGGCCGACGA |
| | GAGAAAGGGAATTTC | AGGGTCCCCGACCTC | GCTCTGGCCGACGAG |
| | AGAAAGGGAATTTCA | GGGTCCCCGACCTCG | CTCTGGCCGACGAGT |
| | GAAAGGGAATTTCAT | GGTCCCCGACCTCGC | TCTGGCCGACGAGTG |
| | AAAGGGAATTTCATC | GTCCCCGACCTCGCT | CTGGCCGACGAGTGG |
| 10 | AAGGGAATTTCATCC | TCCCCGACCTCGCTG | TGGCCGACGAGTGGA |
| | AGGGAATTTCATCCC | CCCCGACCTCGCTGT | GGCCGACGAGTGGAG |
| | GGGAATTTCATCCCA | CCCGACCTCGCTGTG | GCCGACGAGTGGAGA |
| | GGAATTTCATCCCAA | CCGACCTCGCTGTGG | CCGACGAGTGGAGAA |
| | GAATTTCATCCCAAA | CGACCTCGCTGTGGG | CGACGAGTGGAGAAA |
| 15 | AATTTCATCCCAAAT | GACCTCGCTGTGGGG | GACGAGTGGAGAAAT |
| | ATTTCATCCCAAATA | ACCTCGCTGTGGGGG | ACGAGTGGAGAAATC |
| | TTTCATCCCAAATAA | CCTCGCTGTGGGGGC | CGAGTGGAGAAATCT |
| | TTCATCCCAAATAAA | CTCGCTGTGGGGGCT | GAGTGGAGAAATCTG |
| | TCATCCCAAATAAAA | TCGCTGTGGGGGCTC | AGTGGAGAAATCTGC |
| 20 | CATCCCAAATAAAAG | CGCTGTGGGGGCTCC | GTGGAGAAATCTGCG |
| | ATCCCAAATAAAAGG | GCTGTGGGGGCTCCT | TGGAGAAATCTGCGG |
| | TCCCAAATAAAAGGA | CTGTGGGGGCTCCTG | GGAGAAATCTGCGGG |
| | CCCAAATAAAAGGAA | TGTGGGGGCTCCTGT | GAGAAATCTGCGGGC |
| | CCAAATAAAAGGAAT | GTGGGGGCTCCTGTT | AGAAATCTGCGGGCC |
| 25 | CAAATAAAAGGAATG | TGGGGGCTCCTGTTT | GAAATCTGCGGGCCA |
| | AAATAAAAGGAATGA | GGGGGCTCCTGTTTC | AAATCTGCGGGCCAG |
| | AATAAAAGGAATGAA | GGGGCTCCTGTTTCT | AATCTGCGGGCCAGG |
| | ATAAAAGGAATGAAG | GGGCTCCTGTTTCTC | ATCTGCGGGCCAGGC |
| | TAAAAGGAATGAAGT | GGCTCCTGTTTCTCT | TCTGCGGGCCAGGCA |
| 30 | AAAAGGAATGAAGTC | GCTCCTGTTTCTCTC | CTGCGGGCCAGGCAT |
| | AAAGGAATGAAGTCT | CTCCTGTTTCTCTCC | TGCGGGCCAGGCATC |
| | AAGGAATGAAGTCTG | TCCTGTTTCTCTCCG | GCGGGCCAGGCATCG |
| | AGGAATGAAGTCTGG | CCTGTTTCTCTCCGC | CGGGCCAGGCATCGA |
| | GGAATGAAGTCTGGC | CTGTTTCTCTCCGCC | GGGCCAGGCATCGAC |
| 35 | GAATGAAGTCTGGCT | TGTTTCTCTCCGCCG | GGCCAGGCATCGACA |
| | AATGAAGTCTGGCTC | GTTTCTCTCCGCCGC | GCCAGGCATCGACAT |
| | ATGAAGTCTGGCTCC | TTTCTCTCCGCCGCG | CCAGGCATCGACATC |
| | TGAAGTCTGGCTCCG | TTCTCTCCGCCGCGC | CAGGCATCGACATCC |
| | GAAGTCTGGCTCCGG | TCTCTCCGCCGCGCT | AGGCATCGACATCCG |
| 40 | AAGTCTGGCTCCGGA | CTCTCCGCCGCGCTC | GGCATCGACATCCGC |
| | AGTCTGGCTCCGGAG | TCTCCGCCGCGCTCT | GCATCGACATCCGCA |
| | GTCTGGCTCCGGAGG | CTCCGCCGCGCTCTC | CATCGACATCCGCAA |
| | TCTGGCTCCGGAGGA | TCCGCCGCGCTCTCG | ATCGACATCCGCAAC |
| | CTGGCTCCGGAGGAG | CCGCCGCGCTCTCGC | TCGACATCCGCAACG |
| 45 | TGGCTCCGGAGGAGG | CGCCGCGCTCTCGCT | CGACATCCGCAACGA |
| | GGCTCCGGAGGAGGG | GCCGCGCTCTCGCTC | GACATCCGCAACGAC |
| | GCTCCGGAGGAGGGT | CCGCGCTCTCGCTCT | ACATCCGCAACGACT |
| | CTCCGGAGGAGGGTC | CGCGCTCTCGCTCTG | CATCCGCAACGACTA |
| | TCCGGAGGAGGGTCC | GCGCTCTCGCTCTGG | ATCCGCAACGACTAT |
| 50 | CCGGAGGAGGGTCCC | CGCTCTCGCTCTGGC | TCCGCAACGACTATC |
| | CGGAGGAGGGTCCCC | GCTCTCGCTCTGGCC | CCGCAACGACTATCA |

| | | |
|---|---|---|
| CGCAACGACTATCAG | GGCTACCTCCACATC | CGCTTCCCCAAGCTC |
| GCAACGACTATCAGC | GCTACCTCCACATCC | GCTTCCCCAAGCTCA |
| CAACGACTATCAGCA | CTACCTCCACATCCT | CTTCCCCAAGCTCAC |
| AACGACTATCAGCAG | TACCTCCACATCCTG | TTCCCCAAGCTCACG |
| ACGACTATCAGCAGC | ACCTCCACATCCTGC | TCCCCAAGCTCACGG |
| CGACTATCAGCAGCT | CCTCCACATCCTGCT | CCCCAAGCTCACGGT |
| GACTATCAGCAGCTG | CTCCACATCCTGCTC | CCCAAGCTCACGGTC |
| ACTATCAGCAGCTGA | TCCACATCCTGCTCA | CCAAGCTCACGGTCA |
| CTATCAGCAGCTGAA | CCACATCCTGCTCAT | CAAGCTCACGGTCAT |
| TATCAGCAGCTGAAG | CACATCCTGCTCATC | AAGCTCACGGTCATT |
| ATCAGCAGCTGAAGC | ACATCCTGCTCATCT | AGCTCACGGTCATTA |
| TCAGCAGCTGAAGCG | CATCCTGCTCATCTC | GCTCACGGTCATTAC |
| CAGCAGCTGAAGCGC | ATCCTGCTCATCTCC | CTCACGGTCATTACC |
| AGCAGCTGAAGCGCC | TCCTGCTCATCTCCA | TCACGGTCATTACCG |
| GCAGCTGAAGCGCCT | CCTGCTCATCTCCAA | CACGGTCATTACCGA |
| CAGCTGAAGCGCCTG | CTGCTCATCTCCAAG | ACGGTCATTACCGAG |
| AGCTGAAGCGCCTGG | TGCTCATCTCCAAGG | CGGTCATTACCGAGT |
| GCTGAAGCGCCTGGA | GCTCATCTCCAAGGC | GGTCATTACCGAGTA |
| CTGAAGCGCCTGGAG | CTCATCTCCAAGGCC | GTCATTACCGAGTAC |
| TGAAGCGCCTGGAGA | TCATCTCCAAGGCCG | TCATTACCGAGTACT |
| GAAGCGCCTGGAGAA | CATCTCCAAGGCCGA | CATTACCGAGTACTT |
| AAGCGCCTGGAGAAC | ATCTCCAAGGCCGAG | ATTACCGAGTACTTG |
| AGCGCCTGGAGAACT | TCTCCAAGGCCGAGG | TTACCGAGTACTTGC |
| GCGCCTGGAGAACTG | CTCCAAGGCCGAGGA | TACCGAGTACTTGCT |
| CGCCTGGAGAACTGC | TCCAAGGCCGAGGAC | ACCGAGTACTTGCTG |
| GCCTGGAGAACTGCA | CCAAGGCCGAGGACT | CCGAGTACTTGCTGC |
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| GAACTGCACGGTGAT | CGAGGACTACCGCAG | CTTGCTGCTGTTCCG |
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| ACTGCACGGTGATCG | AGGACTACCGCAGCT | TGCTGCTGTTCCGAG |
| CTGCACGGTGATCGA | GGACTACCGCAGCTA | GCTGCTGTTCCGAGT |
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| TGATCGAGGGCTACC | GCAGCTACCGCTTCC | TCCGAGTGGCTGGCC |
| GATCGAGGGCTACCT | CAGCTACCGCTTCCC | CCGAGTGGCTGGCCT |
| ATCGAGGGCTACCTC | AGCTACCGCTTCCCC | CGAGTGGCTGGCCTC |
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| CGAGGGCTACCTCCA | CTACCGCTTCCCCAA | AGTGGCTGGCCTCGA |
| GAGGGCTACCTCCAC | TACCGCTTCCCCAAG | GTGGCTGGCCTCGAG |
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| | GCTGGCCTCGAGAGC | GGCTGGAAACTCTTC | CTCAAGGATATTGGG |
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| | TGGCCTCGAGAGCCT | CTGGAAACTCTTCTA | CAAGGATATTGGGCT |
| | GGCCTCGAGAGCCTC | TGGAAACTCTTCTAC | AAGGATATTGGGCTT |
| 5 | GCCTCGAGAGCCTCG | GGAAACTCTTCTACA | AGGATATTGGGCTTT |
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| | CTCGAGAGCCTCGGA | AAACTCTTCTACAAC | GATATTGGGCTTTAC |
| | TCGAGAGCCTCGGAG | AACTCTTCTACAACT | ATATTGGGCTTTACA |
| | CGAGAGCCTCGGAGA | ACTCTTCTACAACTA | TATTGGGCTTTACAA |
| 10 | GAGAGCCTCGGAGAC | CTCTTCTACAACTAC | ATTGGGCTTTACAAC |
| | AGAGCCTCGGAGACC | TCTTCTACAACTACG | TTGGGCTTTACAACC |
| | GAGCCTCGGAGACCT | CTTCTACAACTACGC | TGGGCTTTACAACCT |
| | AGCCTCGGAGACCTC | TTCTACAACTACGCC | GGGCTTTACAACCTG |
| | GCCTCGGAGACCTCT | TCTACAACTACGCCC | GGCTTTACAACCTGA |
| 15 | CCTCGGAGACCTCTT | CTACAACTACGCCCT | GCTTTACAACCTGAG |
| | CTCGGAGACCTCTTC | TACAACTACGCCCTG | CTTTACAACCTGAGG |
| | TCGGAGACCTCTTCC | ACAACTACGCCCTGG | TTTACAACCTGAGGA |
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| | GGAGACCTCTTCCCC | AACTACGCCCTGGTC | TACAACCTGAGGAAC |
| 20 | GAGACCTCTTCCCCA | ACTACGCCCTGGTCA | ACAACCTGAGGAACA |
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| | GACCTCTTCCCCAAC | TACGCCCTGGTCATC | AACCTGAGGAACATT |
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| 30 | CCCCAACCTCACGGT | GGTCATCTTCGAGAT | GAACATTACTCGGGG |
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| 35 | ACCTCACGGTCATCC | TCTTCGAGATGACCA | TTACTCGGGGGGCCA |
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| 40 | ACGGTCATCCGCGGC | GAGATGACCAATCTC | CGGGGGGCCATCAGG |
| | CGGTCATCCGCGGCT | AGATGACCAATCTCA | GGGGGGCCATCAGGA |
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| 50 | GCGGCTGGAAACTCT | ATCTCAAGGATATTG | TCAGGATTGAGAAAA |
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| | ATTGAGAAAAATGCT | ATCCTGGATGCGGTG | GAATGTGGGGACCTG |
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| | GAGAAAAATGCTGAC | CTGGATGCGGTGTCC | TGTGGGGACCTGTGT |
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| | GAAAAATGCTGACCT | GGATGCGGTGTCCAA | TGGGGACCTGTGTCC |
| 10 | AAAAATGCTGACCTC | GATGCGGTGTCCAAT | GGGGACCTGTGTCCA |
| | AAAATGCTGACCTCT | ATGCGGTGTCCAATA | GGGACCTGTGTCCAG |
| | AAATGCTGACCTCTG | TGCGGTGTCCAATAA | GGACCTGTGTCCAGG |
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| 25 | TGTTACCTCTCCACT | AACTACATTGTGGGG | GGGACCATGGAGGAG |
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| | TACCTCTCCACTGTG | TACATTGTGGGGAAT | ACCATGGAGGAGAAG |
| | ACCTCTCCACTGTGG | ACATTGTGGGGAATA | CCATGGAGGAGAAGC |
| 30 | CCTCTCCACTGTGGA | CATTGTGGGGAATAA | CATGGAGGAGAAGCC |
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| | TCCACTGTGGACTGG | GTGGGGAATAAGCCC | GAGGAGAAGCCGATG |
| 35 | CCACTGTGGACTGGT | TGGGGAATAAGCCCC | AGGAGAAGCCGATGT |
| | CACTGTGGACTGGTC | GGGGAATAAGCCCCC | GGAGAAGCCGATGTG |
| | ACTGTGGACTGGTCC | GGGAATAAGCCCCCA | GAGAAGCCGATGTGT |
| | CTGTGGACTGGTCCC | GGAATAAGCCCCCAA | AGAAGCCGATGTGTG |
| | TGTGGACTGGTCCCT | GAATAAGCCCCCAAA | GAAGCCGATGTGTGA |
| 40 | GTGGACTGGTCCCTG | AATAAGCCCCCAAAG | AAGCCGATGTGTGAG |
| | TGGACTGGTCCCTGA | ATAAGCCCCCAAAGG | AGCCGATGTGTGAGA |
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| 45 | CTGGTCCCTGATCCT | GCCCCCAAAGGAATG | GATGTGTGAGAAGAC |
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| 50 | CCCTGATCCTGGATG | CAAAGGAATGTGGGG | GTGAGAAGACCACCA |
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| GAGAAGACCACCATC | CGCTGCCAGAAAATG | AACAATGAGTGCTGC |
| AGAAGACCACCATCA | GCTGCCAGAAAATGT | ACAATGAGTGCTGCC |
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| AGACCACCATCAACA | GCCAGAAAATGTGCC | ATGAGTGCTGCCACC |
| GACCACCATCAACAA | CCAGAAAATGTGCCC | TGAGTGCTGCCACCC |
| ACCACCATCAACAAT | CAGAAAATGTGCCCA | GAGTGCTGCCACCCC |
| CCACCATCAACAATG | AGAAAATGTGCCCAA | AGTGCTGCCACCCCG |
| CACCATCAACAATGA | GAAAATGTGCCCAAG | GTGCTGCCACCCCGA |
| ACCATCAACAATGAG | AAAATGTGCCCAAGC | TGCTGCCACCCCGAG |
| CCATCAACAATGAGT | AAATGTGCCCAAGCA | GCTGCCACCCCGAGT |
| CATCAACAATGAGTA | AATGTGCCCAAGCAC | CTGCCACCCCGAGTG |
| ATCAACAATGAGTAC | ATGTGCCCAAGCACG | TGCCACCCCGAGTGC |
| TCAACAATGAGTACA | TGTGCCCAAGCACGT | GCCACCCCGAGTGCC |
| CAACAATGAGTACAA | GTGCCCAAGCACGTG | CCACCCCGAGTGCCT |
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| ACCGCTGCCAGAAAA | AGAACAATGAGTGCT | ACAACGACACGGCCT |
| CCGCTGCCAGAAAAT | GAACAATGAGTGCTG | CAACGACACGGCCTG |

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| | ACGGCCTGTGTAGCT | GCCTGCCCGCCCAAC | GACTTCTGCGCCAAC |
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| | GGCCTGTGTAGCTTG | CTGCCCGCCCAACAC | CTTCTGCGCCAACAT |
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| 20 | CTTGCCGCCACTACT | ACACCTACAGGTTTG | ACATCCTCAGCGCCG |
| | TTGCCGCCACTACTA | CACCTACAGGTTTGA | CATCCTCAGCGCCGA |
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| | CCGCCACTACTACTA | CTACAGGTTTGAGGG | CCTCAGCGCCGAGAG |
| 25 | CGCCACTACTACTAT | TACAGGTTTGAGGGC | CTCAGCGCCGAGAGC |
| | GCCACTACTACTATG | ACAGGTTTGAGGGCT | TCAGCGCCGAGAGCA |
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| | CACTACTACTATGCC | AGGTTTGAGGGCTGG | AGCGCCGAGAGCAGC |
| | ACTACTACTATGCCG | GGTTTGAGGGCTGGC | GCGCCGAGAGCAGCG |
| 30 | CTACTACTATGCCGG | GTTTGAGGGCTGGCG | CGCCGAGAGCAGCGA |
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| | GTCTGTGTGCCTGCC | TGTGTGGACCGTGAC | TCCGAGGGGTTTGTG |
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| 50 | GTGTGCCTGCCTGCC | TGGACCGTGACTTCT | AGGGGTTTGTGATCC |
| | TGTGCCTGCCTGCCC | GGACCGTGACTTCTG | GGGGTTTGTGATCCA |

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| | GATCCACGACGGCGA | CGGCAGCCAGAGCAT | CTGTGAGGAAGAAAA |
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| | CGAGTGCATGCAGGA | CATGTACTGCATCCC | AAAGAAAACAAAGAC |
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| | GTGCATGCAGGAGTG | GTACTGCATCCCTTG | GAAAACAAAGACCAT |
| 25 | TGCATGCAGGAGTGC | TACTGCATCCCTTGT | AAAACAAAGACCATT |
| | GCATGCAGGAGTGCC | ACTGCATCCCTTGTG | AAACAAAGACCATTG |
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| | GAGTGCCCCTCGGGC | CCTTGTGAAGGTCCT | ACCATTGATTCTGTT |
| 35 | AGTGCCCCTCGGGCT | CTTGTGAAGGTCCTT | CCATTGATTCTGTTA |
| | GTGCCCCTCGGGCTT | TTGTGAAGGTCCTTG | CATTGATTCTGTTAC |
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| 45 | GGGCTTCATCCGCAA | TCCTTGCCCGAAGGT | TGTTACTTCTGCTCA |
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| | GCTTCATCCGCAACG | CTTGCCCGAAGGTCT | TTACTTCTGCTCAGA |
| | CTTCATCCGCAACGG | TTGCCCGAAGGTCTG | TACTTCTGCTCAGAT |
| | TTCATCCGCAACGGC | TGCCCGAAGGTCTGT | ACTTCTGCTCAGATG |
| 50 | TCATCCGCAACGGCA | GCCCGAAGGTCTGTG | CTTCTGCTCAGATGC |
| | CATCCGCAACGGCAG | CCCGAAGGTCTGTGA | TTCTGCTCAGATGCT |

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|---|---|---|---|
| | TCTGCTCAGATGCTC | AACATCCGACGGGGG | CTCATCGAGGTGGTG |
| | CTGCTCAGATGCTCC | ACATCCGACGGGGGA | TCATCGAGGTGGTGA |
| | TGCTCAGATGCTCCA | CATCCGACGGGGGAA | CATCGAGGTGGTGAC |
| | GCTCAGATGCTCCAA | ATCCGACGGGGGAAT | ATCGAGGTGGTGACG |
| 5 | CTCAGATGCTCCAAG | TCCGACGGGGGAATA | TCGAGGTGGTGACGG |
| | TCAGATGCTCCAAGG | CCGACGGGGGAATAA | CGAGGTGGTGACGGG |
| | CAGATGCTCCAAGGA | CGACGGGGGAATAAC | GAGGTGGTGACGGGC |
| | AGATGCTCCAAGGAT | GACGGGGGAATAACA | AGGTGGTGACGGGCT |
| | GATGCTCCAAGGATG | ACGGGGGAATAACAT | GGTGGTGACGGGCTA |
| 10 | ATGCTCCAAGGATGC | CGGGGGAATAACATT | GTGGTGACGGGCTAC |
| | TGCTCCAAGGATGCA | GGGGGAATAACATTG | TGGTGACGGGCTACG |
| | GCTCCAAGGATGCAC | GGGGAATAACATTGC | GGTGACGGGCTACGT |
| | CTCCAAGGATGCACC | GGGAATAACATTGCT | GTGACGGGCTACGTG |
| | TCCAAGGATGCACCA | GGAATAACATTGCTT | TGACGGGCTACGTGA |
| 15 | CCAAGGATGCACCAT | GAATAACATTGCTTC | GACGGGCTACGTGAA |
| | CAAGGATGCACCATC | AATAACATTGCTTCA | ACGGGCTACGTGAAG |
| | AAGGATGCACCATCT | ATAACATTGCTTCAG | CGGGCTACGTGAAGA |
| | AGGATGCACCATCTT | TAACATTGCTTCAGA | GGGCTACGTGAAGAT |
| | GGATGCACCATCTTC | AACATTGCTTCAGAG | GGCTACGTGAAGATC |
| 20 | GATGCACCATCTTCA | ACATTGCTTCAGAGC | GCTACGTGAAGATCC |
| | ATGCACCATCTTCAA | CATTGCTTCAGAGCT | CTACGTGAAGATCCG |
| | TGCACCATCTTCAAG | ATTGCTTCAGAGCTG | TACGTGAAGATCCGC |
| | GCACCATCTTCAAGG | TTGCTTCAGAGCTGG | ACGTGAAGATCCGCC |
| | CACCATCTTCAAGGG | TGCTTCAGAGCTGGA | CGTGAAGATCCGCCA |
| 25 | ACCATCTTCAAGGGC | GCTTCAGAGCTGGAG | GTGAAGATCCGCCAT |
| | CCATCTTCAAGGGCA | CTTCAGAGCTGGAGA | TGAAGATCCGCCATT |
| | CATCTTCAAGGGCAA | TTCAGAGCTGGAGAA | GAAGATCCGCCATTC |
| | ATCTTCAAGGGCAAT | TCAGAGCTGGAGAAC | AAGATCCGCCATTCT |
| | TCTTCAAGGGCAATT | CAGAGCTGGAGAACT | AGATCCGCCATTCTC |
| 30 | CTTCAAGGGCAATTT | AGAGCTGGAGAACTT | GATCCGCCATTCTCA |
| | TTCAAGGGCAATTTG | GAGCTGGAGAACTTC | ATCCGCCATTCTCAT |
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| | CAAGGGCAATTTGCT | GCTGGAGAACTTCAT | CCGCCATTCTCATGC |
| | AAGGGCAATTTGCTC | CTGGAGAACTTCATG | CGCCATTCTCATGCC |
| 35 | AGGGCAATTTGCTCA | TGGAGAACTTCATGG | GCCATTCTCATGCCT |
| | GGGCAATTTGCTCAT | GGAGAACTTCATGGG | CCATTCTCATGCCTT |
| | GGCAATTTGCTCATT | GAGAACTTCATGGGG | CATTCTCATGCCTTG |
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| | CAATTTGCTCATTAA | GAACTTCATGGGGCT | TTCTCATGCCTTGGT |
| 40 | AATTTGCTCATTAAC | AACTTCATGGGGCTC | TCTCATGCCTTGGTC |
| | ATTTGCTCATTAACA | ACTTCATGGGGCTCA | CTCATGCCTTGGTCT |
| | TTTGCTCATTAACAT | CTTCATGGGGCTCAT | TCATGCCTTGGTCTC |
| | TTGCTCATTAACATC | TTCATGGGGCTCATC | CATGCCTTGGTCTCC |
| | TGCTCATTAACATCC | TCATGGGGCTCATCG | ATGCCTTGGTCTCCT |
| 45 | GCTCATTAACATCCG | CATGGGGCTCATCGA | TGCCTTGGTCTCCTT |
| | CTCATTAACATCCGA | ATGGGGCTCATCGAG | GCCTTGGTCTCCTTG |
| | TCATTAACATCCGAC | TGGGGCTCATCGAGG | CCTTGGTCTCCTTGT |
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| | ATTAACATCCGACGG | GGGCTCATCGAGGTG | TTGGTCTCCTTGTCC |
| 50 | TTAACATCCGACGGG | GGCTCATCGAGGTGG | TGGTCTCCTTGTCCT |
| | TAACATCCGACGGGG | GCTCATCGAGGTGGT | GGTCTCCTTGTCCTT |

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|---|---|---|---|
| | GTCTCCTTGTCCTTC | CTAGAAGGGAATTAC | CTGTGGGACTGGGAC |
| | TCTCCTTGTCCTTCC | TAGAAGGGAATTACT | TGTGGGACTGGGACC |
| | CTCCTTGTCCTTCCT | AGAAGGGAATTACTC | GTGGGACTGGGACCA |
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| 5 | CCTTGTCCTTCCTAA | AAGGGAATTACTCCT | GGGACTGGGACCACC |
| | CTTGTCCTTCCTAAA | AGGGAATTACTCCTT | GGACTGGGACCACCG |
| | TTGTCCTTCCTAAAA | GGGAATTACTCCTTC | GACTGGGACCACCGC |
| | TGTCCTTCCTAAAAA | GGAATTACTCCTTCT | ACTGGGACCACCGCA |
| | GTCCTTCCTAAAAAA | GAATTACTCCTTCTA | CTGGGACCACCGCAA |
| 10 | TCCTTCCTAAAAAAC | AATTACTCCTTCTAC | TGGGACCACCGCAAC |
| | CCTTCCTAAAAAACC | ATTACTCCTTCTACG | GGGACCACCGCAACC |
| | CTTCCTAAAAAACCT | TTACTCCTTCTACGT | GGACCACCGCAACCT |
| | TTCCTAAAAAACCTT | TACTCCTTCTACGTC | GACCACCGCAACCTG |
| | TCCTAAAAAACCTTC | ACTCCTTCTACGTCC | ACCACCGCAACCTGA |
| 15 | CCTAAAAAACCTTCG | CTCCTTCTACGTCCT | CCACCGCAACCTGAC |
| | CTAAAAAACCTTCGC | TCCTTCTACGTCCTC | CACCGCAACCTGACC |
| | TAAAAAACCTTCGCC | CCTTCTACGTCCTCG | ACCGCAACCTGACCA |
| | AAAAAACCTTCGCCT | CTTCTACGTCCTCGA | CCGCAACCTGACCAT |
| | AAAAACCTTCGCCTC | TTCTACGTCCTCGAC | CGCAACCTGACCATC |
| 20 | AAAACCTTCGCCTCA | TCTACGTCCTCGACA | GCAACCTGACCATCA |
| | AAACCTTCGCCTCAT | CTACGTCCTCGACAA | CAACCTGACCATCAA |
| | AACCTTCGCCTCATC | TACGTCCTCGACAAC | AACCTGACCATCAAA |
| | ACCTTCGCCTCATCC | ACGTCCTCGACAACC | ACCTGACCATCAAAG |
| | CCTTCGCCTCATCCT | CGTCCTCGACAACCA | CCTGACCATCAAAGC |
| 25 | CTTCGCCTCATCCTA | GTCCTCGACAACCAG | CTGACCATCAAAGCA |
| | TTCGCCTCATCCTAG | TCCTCGACAACCAGA | TGACCATCAAAGCAG |
| | TCGCCTCATCCTAGG | CCTCGACAACCAGAA | GACCATCAAAGCAGG |
| | CGCCTCATCCTAGGA | CTCGACAACCAGAAC | ACCATCAAAGCAGGG |
| | GCCTCATCCTAGGAG | TCGACAACCAGAACT | CCATCAAAGCAGGGA |
| 30 | CCTCATCCTAGGAGA | CGACAACCAGAACTT | CATCAAAGCAGGGAA |
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| | ATCCTAGGAGAGGAG | AACCAGAACTTGCAG | AAAGCAGGGAAAATG |
| 35 | TCCTAGGAGAGGAGC | ACCAGAACTTGCAGC | AAGCAGGGAAAATGT |
| | CCTAGGAGAGGAGCA | CCAGAACTTGCAGCA | AGCAGGGAAAATGTA |
| | CTAGGAGAGGAGCAG | CAGAACTTGCAGCAA | GCAGGGAAAATGTAC |
| | TAGGAGAGGAGCAGC | AGAACTTGCAGCAAC | CAGGGAAAATGTACT |
| | AGGAGAGGAGCAGCT | GAACTTGCAGCAACT | AGGGAAAATGTACTT |
| 40 | GGAGAGGAGCAGCTA | AACTTGCAGCAACTG | GGGAAAATGTACTTT |
| | GAGAGGAGCAGCTAG | ACTTGCAGCAACTGT | GGAAAATGTACTTTG |
| | AGAGGAGCAGCTAGA | CTTGCAGCAACTGTG | GAAAATGTACTTTGC |
| | GAGGAGCAGCTAGAA | TTGCAGCAACTGTGG | AAAATGTACTTTGCT |
| | AGGAGCAGCTAGAAG | TGCAGCAACTGTGGG | AAATGTACTTTGCTT |
| 45 | GGAGCAGCTAGAAGG | GCAGCAACTGTGGGA | AATGTACTTTGCTTT |
| | GAGCAGCTAGAAGGG | CAGCAACTGTGGGAC | ATGTACTTTGCTTTC |
| | AGCAGCTAGAAGGGA | AGCAACTGTGGGACT | TGTACTTTGCTTTCA |
| | GCAGCTAGAAGGGAA | GCAACTGTGGGACTG | GTACTTTGCTTTCAA |
| | CAGCTAGAAGGGAAT | CAACTGTGGGACTGG | TACTTTGCTTTCAAT |
| 50 | AGCTAGAAGGGAATT | AACTGTGGGACTGGG | ACTTTGCTTTCAATC |
| | GCTAGAAGGGAATTA | ACTGTGGGACTGGGA | CTTTGCTTTCAATCC |

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|---|---|---|
| TTTGCTTTCAATCCC | GTGACGGGGACTAAA | AACGGGGAGAGAGCC |
| TTGCTTTCAATCCCA | TGACGGGGACTAAAG | ACGGGGAGAGAGCCT |
| TGCTTTCAATCCCAA | GACGGGGACTAAAGG | CGGGGAGAGAGCCTC |
| GCTTTCAATCCCAAA | ACGGGGACTAAAGGG | GGGGAGAGAGCCTCC |
| CTTTCAATCCCAAAT | CGGGGACTAAAGGGC | GGGAGAGAGCCTCCT |
| TTTCAATCCCAAATT | GGGGACTAAAGGGCG | GGAGAGAGCCTCCTG |
| TTCAATCCCAAATTA | GGGACTAAAGGGCGC | GAGAGAGCCTCCTGT |
| TCAATCCCAAATTAT | GGACTAAAGGGCGCC | AGAGAGCCTCCTGTG |
| CAATCCCAAATTATG | GACTAAAGGGCGCCA | GAGAGCCTCCTGTGA |
| AATCCCAAATTATGT | ACTAAAGGGCGCCAA | AGAGCCTCCTGTGAA |
| ATCCCAAATTATGTG | CTAAAGGGCGCCAAA | GAGCCTCCTGTGAAA |
| TCCCAAATTATGTGT | TAAAGGGCGCCAAAG | AGCCTCCTGTGAAAG |
| CCCAAATTATGTGTT | AAAGGGCGCCAAAGC | GCCTCCTGTGAAAGT |
| CCAAATTATGTGTTT | AAGGGCGCCAAAGCA | CCTCCTGTGAAAGTG |
| CAAATTATGTGTTTC | AGGGCGCCAAAGCAA | CTCCTGTGAAAGTGA |
| AAATTATGTGTTTCC | GGGCGCCAAAGCAAA | TCCTGTGAAAGTGAC |
| AATTATGTGTTTCCG | GGCGCCAAAGCAAAG | CCTGTGAAAGTGACG |
| ATTATGTGTTTCCGA | GCGCCAAAGCAAAGG | CTGTGAAAGTGACGT |
| TTATGTGTTTCCGAA | CGCCAAAGCAAAGGG | TGTGAAAGTGACGTC |
| TATGTGTTTCCGAAA | GCCAAAGCAAAGGGG | GTGAAAGTGACGTCC |
| ATGTGTTTCCGAAAT | CCAAAGCAAAGGGGA | TGAAAGTGACGTCCT |
| TGTGTTTCCGAAATT | CAAAGCAAAGGGGAC | GAAAGTGACGTCCTG |
| GTGTTTCCGAAATTT | AAAGCAAAGGGGACA | AAAGTGACGTCCTGC |
| TGTTTCCGAAATTTA | AAGCAAAGGGGACAT | AAGTGACGTCCTGCA |
| GTTTCCGAAATTTAC | AGCAAAGGGGACATA | AGTGACGTCCTGCAT |
| TTTCCGAAATTTACC | GCAAAGGGGACATAA | GTGACGTCCTGCATT |
| TTCCGAAATTTACCG | CAAAGGGGACATAAA | TGACGTCCTGCATTT |
| TCCGAAATTTACCGC | AAAGGGGACATAAAC | GACGTCCTGCATTTC |
| CCGAAATTTACCGCA | AAGGGGACATAAACA | ACGTCCTGCATTTCA |
| CGAAATTTACCGCAT | AGGGGACATAAACAC | CGTCCTGCATTTCAC |
| GAAATTTACCGCATG | GGGGACATAAACACC | GTCCTGCATTTCACC |
| AAATTTACCGCATGG | GGGACATAAACACCA | TCCTGCATTTCACCT |
| AATTTACCGCATGGA | GGACATAAACACCAG | CCTGCATTTCACCTC |
| ATTTACCGCATGGAG | GACATAAACACCAGG | CTGCATTTCACCTCC |
| TTTACCGCATGGAGG | ACATAAACACCAGGA | TGCATTTCACCTCCA |
| TTACCGCATGGAGGA | CATAAACACCAGGAA | GCATTTCACCTCCAC |
| TACCGCATGGAGGAA | ATAAACACCAGGAAC | CATTTCACCTCCACC |
| ACCGCATGGAGGAAG | TAAACACCAGGAACA | ATTTCACCTCCACCA |
| CCGCATGGAGGAAGT | AAACACCAGGAACAA | TTTCACCTCCACCAC |
| CGCATGGAGGAAGTG | AACACCAGGAACAAC | TTCACCTCCACCACC |
| GCATGGAGGAAGTGA | ACACCAGGAACAACG | TCACCTCCACCACCA |
| CATGGAGGAAGTGAC | CACCAGGAACAACGG | CACCTCCACCACCAC |
| ATGGAGGAAGTGACG | ACCAGGAACAACGGG | ACCTCCACCACCACG |
| TGGAGGAAGTGACGG | CCAGGAACAACGGGG | CCTCCACCACCACGT |
| GGAGGAAGTGACGGG | CAGGAACAACGGGGA | CTCCACCACCACGTC |
| GAGGAAGTGACGGGG | AGGAACAACGGGGAG | TCCACCACCACGTCG |
| AGGAAGTGACGGGGA | GGAACAACGGGGAGA | CCACCACCACGTCGA |
| GGAAGTGACGGGGAC | GAACAACGGGGAGAG | CACCACCACGTCGAA |
| GAAGTGACGGGGACT | AACAACGGGGAGAGA | ACCACCACGTCGAAG |
| AAGTGACGGGGACTA | ACAACGGGGAGAGAG | CCACCACGTCGAAGA |
| AGTGACGGGGACTAA | CAACGGGGAGAGAGC | CACCACGTCGAAGAA |

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|---|---|---|---|
| | ACCACGTCGAAGAAT | GACTACAGGGATCTC | AAGAATGTCACAGAG |
| | CCACGTCGAAGAATC | ACTACAGGGATCTCA | AGAATGTCACAGAGT |
| | CACGTCGAAGAATCG | CTACAGGGATCTCAT | GAATGTCACAGAGTA |
| | ACGTCGAAGAATCGC | TACAGGGATCTCATC | AATGTCACAGAGTAT |
| 5 | CGTCGAAGAATCGCA | ACAGGGATCTCATCA | ATGTCACAGAGTATG |
| | GTCGAAGAATCGCAT | CAGGGATCTCATCAG | TGTCACAGAGTATGA |
| | TCGAAGAATCGCATC | AGGGATCTCATCAGC | GTCACAGAGTATGAT |
| | CGAAGAATCGCATCA | GGGATCTCATCAGCT | TCACAGAGTATGATG |
| | GAAGAATCGCATCAT | GGATCTCATCAGCTT | CACAGAGTATGATGG |
| 10 | AAGAATCGCATCATC | GATCTCATCAGCTTC | ACAGAGTATGATGGG |
| | AGAATCGCATCATCA | ATCTCATCAGCTTCA | CAGAGTATGATGGGC |
| | GAATCGCATCATCAT | TCTCATCAGCTTCAC | AGAGTATGATGGGCA |
| | AATCGCATCATCATA | CTCATCAGCTTCACC | GAGTATGATGGGCAG |
| | ATCGCATCATCATAA | TCATCAGCTTCACCG | AGTATGATGGGCAGG |
| 15 | TCGCATCATCATAAC | CATCAGCTTCACCGT | GTATGATGGGCAGGA |
| | CGCATCATCATAACC | ATCAGCTTCACCGTT | TATGATGGGCAGGAT |
| | GCATCATCATAACCT | TCAGCTTCACCGTTT | ATGATGGGCAGGATG |
| | CATCATCATAACCTG | CAGCTTCACCGTTTA | TGATGGGCAGGATGC |
| | ATCATCATAACCTGG | AGCTTCACCGTTTAC | GATGGGCAGGATGCC |
| 20 | TCATCATAACCTGGC | GCTTCACCGTTTACT | ATGGGCAGGATGCCT |
| | CATCATAACCTGGCA | CTTCACCGTTTACTA | TGGGCAGGATGCCTG |
| | ATCATAACCTGGCAC | TTCACCGTTTACTAC | GGGCAGGATGCCTGC |
| | TCATAACCTGGCACC | TCACCGTTTACTACA | GGCAGGATGCCTGCG |
| | CATAACCTGGCACCG | CACCGTTTACTACAA | GCAGGATGCCTGCGG |
| 25 | ATAACCTGGCACCGG | ACCGTTTACTACAAG | CAGGATGCCTGCGGC |
| | TAACCTGGCACCGGT | CCGTTTACTACAAGG | AGGATGCCTGCGGCT |
| | AACCTGGCACCGGTA | CGTTTACTACAAGGA | GGATGCCTGCGGCTC |
| | ACCTGGCACCGGTAC | GTTTACTACAAGGAA | GATGCCTGCGGCTCC |
| | CCTGGCACCGGTACC | TTTACTACAAGGAAG | ATGCCTGCGGCTCCA |
| 30 | CTGGCACCGGTACCG | TTACTACAAGGAAGC | TGCCTGCGGCTCCAA |
| | TGGCACCGGTACCGG | TACTACAAGGAAGCA | GCCTGCGGCTCCAAC |
| | GGCACCGGTACCGGC | ACTACAAGGAAGCAC | CCTGCGGCTCCAACA |
| | GCACCGGTACCGGCC | CTACAAGGAAGCACC | CTGCGGCTCCAACAG |
| | CACCGGTACCGGCCC | TACAAGGAAGCACCC | TGCGGCTCCAACAGC |
| 35 | ACCGGTACCGGCCCC | ACAAGGAAGCACCCT | GCGGCTCCAACAGCT |
| | CCGGTACCGGCCCCC | CAAGGAAGCACCCTT | CGGCTCCAACAGCTG |
| | CGGTACCGGCCCCCT | AAGGAAGCACCCTTT | GGCTCCAACAGCTGG |
| | GGTACCGGCCCCCTG | AGGAAGCACCCTTTA | GCTCCAACAGCTGGA |
| | GTACCGGCCCCCTGA | GGAAGCACCCTTTAA | CTCCAACAGCTGGAA |
| 40 | TACCGGCCCCCTGAC | GAAGCACCCTTTAAG | TCCAACAGCTGGAAC |
| | ACCGGCCCCCTGACT | AAGCACCCTTTAAGA | CCAACAGCTGGAACA |
| | CCGGCCCCCTGACTA | AGCACCCTTTAAGAA | CAACAGCTGGAACAT |
| | CGGCCCCCTGACTAC | GCACCCTTTAAGAAT | AACAGCTGGAACATG |
| | GGCCCCCTGACTACA | CACCCTTTAAGAATG | ACAGCTGGAACATGG |
| 45 | GCCCCCTGACTACAG | ACCCTTTAAGAATGT | CAGCTGGAACATGGT |
| | CCCCCTGACTACAGG | CCCTTTAAGAATGTC | AGCTGGAACATGGTG |
| | CCCCTGACTACAGGG | CCTTTAAGAATGTCA | GCTGGAACATGGTGG |
| | CCCTGACTACAGGGA | CTTTAAGAATGTCAC | CTGGAACATGGTGGA |
| | CCTGACTACAGGGAT | TTTAAGAATGTCACA | TGGAACATGGTGGAC |
| 50 | CTGACTACAGGGATC | TTAAGAATGTCACAG | GGAACATGGTGGACG |
| | TGACTACAGGGATCT | TAAGAATGTCACAGA | GAACATGGTGGACGT |

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|---|---|---|---|
| | AACATGGTGGACGTG | TTACTACATGGGCTG | GTGACCCTCACCATG |
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| | CATGGTGGACGTGGA | ACTACATGGGCTGAA | GACCCTCACCATGGT |
| | ATGGTGGACGTGGAC | CTACATGGGCTGAAG | ACCCTCACCATGGTG |
| 5 | TGGTGGACGTGGACC | TACATGGGCTGAAGC | CCCTCACCATGGTGG |
| | GGTGGACGTGGACCT | ACATGGGCTGAAGCC | CCTCACCATGGTGGA |
| | GTGGACGTGGACCTC | CATGGGCTGAAGCCC | CTCACCATGGTGGAG |
| | TGGACGTGGACCTCC | ATGGGCTGAAGCCCT | TCACCATGGTGGAGA |
| | GGACGTGGACCTCCC | TGGGCTGAAGCCCTG | CACCATGGTGGAGAA |
| 10 | GACGTGGACCTCCCG | GGGCTGAAGCCCTGG | ACCATGGTGGAGAAC |
| | ACGTGGACCTCCCGC | GGCTGAAGCCCTGGA | CCATGGTGGAGAACG |
| | CGTGGACCTCCCGCC | GCTGAAGCCCTGGAC | CATGGTGGAGAACGA |
| | GTGGACCTCCCGCCC | CTGAAGCCCTGGACT | ATGGTGGAGAACGAC |
| | TGGACCTCCCGCCCA | TGAAGCCCTGGACTC | TGGTGGAGAACGACC |
| 15 | GGACCTCCCGCCCAA | GAAGCCCTGGACTCA | GGTGGAGAACGACCA |
| | GACCTCCCGCCCAAC | AAGCCCTGGACTCAG | GTGGAGAACGACCAT |
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| 20 | TCCCGCCCAACAAGG | CCTGGACTCAGTACG | AGAACGACCATATCC |
| | CCCGCCCAACAAGGA | CTGGACTCAGTACGC | GAACGACCATATCCG |
| | CCGCCCAACAAGGAC | TGGACTCAGTACGCC | AACGACCATATCCGT |
| | CGCCCAACAAGGACG | GGACTCAGTACGCCG | ACGACCATATCCGTG |
| | GCCCAACAAGGACGT | GACTCAGTACGCCGT | CGACCATATCCGTGG |
| 25 | CCCAACAAGGACGTG | ACTCAGTACGCCGTT | GACCATATCCGTGGG |
| | CCAACAAGGACGTGG | CTCAGTACGCCGTTT | ACCATATCCGTGGGG |
| | CAACAAGGACGTGGA | TCAGTACGCCGTTTA | CCATATCCGTGGGGC |
| | AACAAGGACGTGGAG | CAGTACGCCGTTTAC | CATATCCGTGGGGCC |
| | ACAAGGACGTGGAGC | AGTACGCCGTTTACG | ATATCCGTGGGGCCA |
| 30 | CAAGGACGTGGAGCC | GTACGCCGTTTACGT | TATCCGTGGGGCCAA |
| | AAGGACGTGGAGCCC | TACGCCGTTTACGTC | ATCCGTGGGGCCAAG |
| | AGGACGTGGAGCCCG | ACGCCGTTTACGTCA | TCCGTGGGGCCAAGA |
| | GGACGTGGAGCCCGG | CGCCGTTTACGTCAA | CCGTGGGGCCAAGAG |
| | GACGTGGAGCCCGGC | GCCGTTTACGTCAAG | CGTGGGGCCAAGAGT |
| 35 | ACGTGGAGCCCGGCA | CCGTTTACGTCAAGG | GTGGGGCCAAGAGTG |
| | CGTGGAGCCCGGCAT | CGTTTACGTCAAGGC | TGGGGCCAAGAGTGA |
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| | GGAGCCCGGCATCTT | TTACGTCAAGGCTGT | GGCCAAGAGTGAGAT |
| 40 | GAGCCCGGCATCTTA | TACGTCAAGGCTGTG | GCCAAGAGTGAGATC |
| | AGCCCGGCATCTTAC | ACGTCAAGGCTGTGA | CCAAGAGTGAGATCT |
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| | CCCGGCATCTTACTA | GTCAAGGCTGTGACC | AAGAGTGAGATCTTG |
| | CCGGCATCTTACTAC | TCAAGGCTGTGACCC | AGAGTGAGATCTTGT |
| 45 | CGGCATCTTACTACA | CAAGGCTGTGACCCT | GAGTGAGATCTTGTA |
| | GGCATCTTACTACAT | AAGGCTGTGACCCTC | AGTGAGATCTTGTAC |
| | GCATCTTACTACATG | AGGCTGTGACCCTCA | GTGAGATCTTGTACA |
| | CATCTTACTACATGG | GGCTGTGACCCTCAC | TGAGATCTTGTACAT |
| | ATCTTACTACATGGG | GCTGTGACCCTCACC | GAGATCTTGTACATT |
| 50 | TCTTACTACATGGGC | CTGTGACCCTCACCA | AGATCTTGTACATTC |
| | CTTACTACATGGGCT | TGTGACCCTCACCAT | GATCTTGTACATTCG |

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|---|---|---|---|
| | ATCTTGTACATTCGC | CTTTCAGCATCGAAC | TCTCTGCCCAACGGC |
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| | CTTGTACATTCGCAC | TTCAGCATCGAACTC | TCTGCCCAACGGCAA |
| | TTGTACATTCGCACC | TCAGCATCGAACTCC | CTGCCCAACGGCAAC |
| 5 | TGTACATTCGCACCA | CAGCATCGAACTCCT | TGCCCAACGGCAACC |
| | GTACATTCGCACCAA | AGCATCGAACTCCTC | GCCCAACGGCAACCT |
| | TACATTCGCACCAAT | GCATCGAACTCCTCT | CCCAACGGCAACCTG |
| | ACATTCGCACCAATG | CATCGAACTCCTCTT | CCAACGGCAACCTGA |
| | CATTCGCACCAATGC | ATCGAACTCCTCTTC | CAACGGCAACCTGAG |
| 10 | ATTCGCACCAATGCT | TCGAACTCCTCTTCT | AACGGCAACCTGAGT |
| | TTCGCACCAATGCTT | CGAACTCCTCTTCTC | ACGGCAACCTGAGTT |
| | TCGCACCAATGCTTC | GAACTCCTCTTCTCA | CGGCAACCTGAGTTA |
| | CGCACCAATGCTTCA | AACTCCTCTTCTCAG | GGCAACCTGAGTTAC |
| | GCACCAATGCTTCAG | ACTCCTCTTCTCAGT | GCAACCTGAGTTACT |
| 15 | CACCAATGCTTCAGT | CTCCTCTTCTCAGTT | CAACCTGAGTTACTA |
| | ACCAATGCTTCAGTT | TCCTCTTCTCAGTTA | AACCTGAGTTACTAC |
| | CCAATGCTTCAGTTC | CCTCTTCTCAGTTAA | ACCTGAGTTACTACA |
| | CAATGCTTCAGTTCC | CTCTTCTCAGTTAAT | CCTGAGTTACTACAT |
| | AATGCTTCAGTTCCT | TCTTCTCAGTTAATC | CTGAGTTACTACATT |
| 20 | ATGCTTCAGTTCCTT | CTTCTCAGTTAATCG | TGAGTTACTACATTG |
| | TGCTTCAGTTCCTTC | TTCTCAGTTAATCGT | GAGTTACTACATTGT |
| | GCTTCAGTTCCTTCC | TCTCAGTTAATCGTG | AGTTACTACATTGTG |
| | CTTCAGTTCCTTCCA | CTCAGTTAATCGTGA | GTTACTACATTGTGC |
| | TTCAGTTCCTTCCAT | TCAGTTAATCGTGAA | TTACTACATTGTGCG |
| 25 | TCAGTTCCTTCCATT | CAGTTAATCGTGAAG | TACTACATTGTGCGC |
| | CAGTTCCTTCCATTC | AGTTAATCGTGAAGT | ACTACATTGTGCGCT |
| | AGTTCCTTCCATTCC | GTTAATCGTGAAGTG | CTACATTGTGCGCTG |
| | GTTCCTTCCATTCCC | TTAATCGTGAAGTGG | TACATTGTGCGCTGG |
| | TTCCTTCCATTCCCT | TAATCGTGAAGTGGA | ACATTGTGCGCTGGC |
| 30 | TCCTTCCATTCCCTT | AATCGTGAAGTGGAA | CATTGTGCGCTGGCA |
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| | CTTCCATTCCCTTGG | TCGTGAAGTGGAACC | TTGTGCGCTGGCAGC |
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| | TCCATTCCCTTGGAC | GTGAAGTGGAACCCT | GTGCGCTGGCAGCGG |
| 35 | CCATTCCCTTGGACG | TGAAGTGGAACCCTC | TGCGCTGGCAGCGGC |
| | CATTCCCTTGGACGT | GAAGTGGAACCCTCC | GCGCTGGCAGCGGCA |
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| 40 | CCCTTGGACGTTCTT | TGGAACCCTCCCTCT | TGGCAGCGGCAGCCT |
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| | TGGACGTTCTTTCAG | ACCCTCCCTCTCTGC | AGCGGCAGCCTCAGG |
| 45 | GGACGTTCTTTCAGC | CCCTCCCTCTCTGCC | GCGGCAGCCTCAGGA |
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| 5 | AGGACGGCTACCTTT | TCAGGAAGTATGCCG | CCAAGACTGAGGTGT |
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| | CGGCTACCTTTACCG | GAAGTATGCCGACGG | GACTGAGGTGTGTGG |
| 10 | GGCTACCTTTACCGG | AAGTATGCCGACGGC | ACTGAGGTGTGTGGT |
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| | CTACCTTTACCGGCA | GTATGCCGACGGCAC | TGAGGTGTGTGGTGG |
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| 35 | GCTCCAAAGACAAAA | TTGAGGAGGTCACAG | GGCCTTGCTGCGCCT |
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| | TGAAGCCGAGAAGCA | TGAGAATTTCCTGCA | GAGAGATGTCATGCA |
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| 35 | AGGAGGCTGAATACC | TCGTGCCCAGACCTG | CCACCATGTCCAGCC |
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| 45 | ATACCGCAAAGTCTT | ACCTGAAAGGAAGCG | CAGCCGAAGCAGGAA |
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| ACACCACGGCCGCAG | CAGAGTACCCTTTCT | TTTCTAACCTTCGGC |
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| ACGGCCGCAGACACC | TACCCTTTCTTTGAG | AACCTTCGGCCTTTC |
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| ACCTACAACATCACC | GAGAGCAGAGTGGAT | TTCACATTGTACCGC |
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| GCTGGAGACAGAGTA | AACTGTCATTTCTAA | CAGCTGCAACCACGA |

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| 5 | GCAACCACGAGGCTG | CAAGGACTATGCCCG | GGGAGCCAAGGCCTG |
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| 10 | CACGAGGCTGAGAAG | ACTATGCCCGCAGAA | CCAAGGCCTGAAAAC |
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| 25 | CTGGGCTGCAGCGCC | GGAGCAGATGACATT | TCCATCTTTTTAAAG |
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| | AGCGCCTCCAACTTC | GACATTCCTGGGCCA | TTAAAGTGGCCGGAA |
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| 50 | TCTTTGCAAGGACTA | TGACCTGGGAGCCAA | CTGAGAATCCCAATG |
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| 40 | TACGGATCACAAGTT | AGGAAGTATGGAGGG | GCCCGGATTCAGGCC |
| | ACGGATCACAAGTTG | GGAAGTATGGAGGGG | CCCGGATTCAGGCCA |
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| | ACATCTCTCTCTGGG | CAGGCCAAAACAGGA | GTCGCTGTCCTGTTG |
| 5 | CATCTCTCTCTGGGA | AGGCCAAAACAGGAT | TCGCTGTCCTGTTGA |
| | ATCTCTCTCTGGGAA | GGCCAAAACAGGATA | CGCTGTCCTGTTGAT |
| | TCTCTCTCTGGGAAT | GCCAAAACAGGATAT | GCTGTCCTGTTGATC |
| | CTCTCTCTGGGAATG | CCAAAACAGGATATG | CTGTCCTGTTGATCG |
| | TCTCTCTGGGAATGG | CAAAACAGGATATGA | TGTCCTGTTGATCGT |
| 10 | CTCTCTGGGAATGGG | AAAACAGGATATGAA | GTCCTGTTGATCGTG |
| | TCTCTGGGAATGGGT | AAACAGGATATGAAA | TCCTGTTGATCGTGG |
| | CTCTGGGAATGGGTC | AACAGGATATGAAAA | CCTGTTGATCGTGGG |
| | TCTGGGAATGGGTCG | ACAGGATATGAAAAC | CTGTTGATCGTGGGA |
| | CTGGGAATGGGTCGT | CAGGATATGAAAACT | TGTTGATCGTGGGAG |
| 15 | TGGGAATGGGTCGTG | AGGATATGAAAACTT | GTTGATCGTGGGAGG |
| | GGGAATGGGTCGTGG | GGATATGAAAACTTC | TTGATCGTGGGAGGG |
| | GGAATGGGTCGTGGA | GATATGAAAACTTCA | TGATCGTGGGAGGGT |
| | GAATGGGTCGTGGAC | ATATGAAAACTTCAT | GATCGTGGGAGGGTT |
| | AATGGGTCGTGGACA | TATGAAAACTTCATC | ATCGTGGGAGGGTTG |
| 20 | ATGGGTCGTGGACAG | ATGAAAACTTCATCC | TCGTGGGAGGGTTGG |
| | TGGGTCGTGGACAGA | TGAAAACTTCATCCA | CGTGGGAGGGTTGGT |
| | GGGTCGTGGACAGAT | GAAAACTTCATCCAT | GTGGGAGGGTTGGTG |
| | GGTCGTGGACAGATC | AAAACTTCATCCATC | TGGGAGGGTTGGTGA |
| | GTCGTGGACAGATCC | AAACTTCATCCATCT | GGGAGGGTTGGTGAT |
| 25 | TCGTGGACAGATCCT | AACTTCATCCATCTG | GGAGGGTTGGTGATT |
| | CGTGGACAGATCCTG | ACTTCATCCATCTGA | GAGGGTTGGTGATTA |
| | GTGGACAGATCCTGT | CTTCATCCATCTGAT | AGGGTTGGTGATTAT |
| | TGGACAGATCCTGTG | TTCATCCATCTGATC | GGGTTGGTGATTATG |
| | GGACAGATCCTGTGT | TCATCCATCTGATCA | GGTTGGTGATTATGC |
| 30 | GACAGATCCTGTGTT | CATCCATCTGATCAT | GTTGGTGATTATGCT |
| | ACAGATCCTGTGTTC | ATCCATCTGATCATC | TTGGTGATTATGCTG |
| | CAGATCCTGTGTTCT | TCCATCTGATCATCG | TGGTGATTATGCTGT |
| | AGATCCTGTGTTCTT | CCATCTGATCATCGC | GGTGATTATGCTGTA |
| | GATCCTGTGTTCTTC | CATCTGATCATCGCT | GTGATTATGCTGTAC |
| 35 | ATCCTGTGTTCTTCT | ATCTGATCATCGCTC | TGATTATGCTGTACG |
| | TCCTGTGTTCTTCTA | TCTGATCATCGCTCT | GATTATGCTGTACGT |
| | CCTGTGTTCTTCTAT | CTGATCATCGCTCTG | ATTATGCTGTACGTC |
| | CTGTGTTCTTCTATG | TGATCATCGCTCTGC | TTATGCTGTACGTCT |
| | TGTGTTCTTCTATGT | GATCATCGCTCTGCC | TATGCTGTACGTCTT |
| 40 | GTGTTCTTCTATGTC | ATCATCGCTCTGCCC | ATGCTGTACGTCTTC |
| | TGTTCTTCTATGTCC | TCATCGCTCTGCCCG | TGCTGTACGTCTTCC |
| | GTTCTTCTATGTCCA | CATCGCTCTGCCCGT | GCTGTACGTCTTCCA |
| | TTCTTCTATGTCCAG | ATCGCTCTGCCCGTC | CTGTACGTCTTCCAT |
| | TCTTCTATGTCCAGG | TCGCTCTGCCCGTCG | TGTACGTCTTCCATA |
| 45 | CTTCTATGTCCAGGC | CGCTCTGCCCGTCGC | GTACGTCTTCCATAG |
| | TTCTATGTCCAGGCC | GCTCTGCCCGTCGCT | TACGTCTTCCATAGA |
| | TCTATGTCCAGGCCA | CTCTGCCCGTCGCTG | ACGTCTTCCATAGAA |
| | CTATGTCCAGGCCAA | TCTGCCCGTCGCTGT | CGTCTTCCATAGAAA |
| | TATGTCCAGGCCAAA | CTGCCCGTCGCTGTC | GTCTTCCATAGAAAG |
| 50 | ATGTCCAGGCCAAAA | TGCCCGTCGCTGTCC | TCTTCCATAGAAAGA |
| | TGTCCAGGCCAAAAC | GCCCGTCGCTGTCCT | CTTCCATAGAAAGAG |

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|---|---|---|---|
| | TTCCATAGAAAGAGA | TCTGTGAACCCGGAG | TGGGAGGTGGCTCGG |
| | TCCATAGAAAGAGAA | CTGTGAACCCGGAGT | GGGAGGTGGCTCGGG |
| | CCATAGAAAGAGAAA | TGTGAACCCGGAGTA | GGAGGTGGCTCGGGA |
| | CATAGAAAGAGAAAT | GTGAACCCGGAGTAC | GAGGTGGCTCGGGAG |
| 5 | ATAGAAAGAGAAATA | TGAACCCGGAGTACT | AGGTGGCTCGGGAGA |
| | TAGAAAGAGAAATAA | GAACCCGGAGTACTT | GGTGGCTCGGGAGAA |
| | AGAAAGAGAAATAAC | AACCCGGAGTACTTC | GTGGCTCGGGAGAAG |
| | GAAAGAGAAATAACA | ACCCGGAGTACTTCA | TGGCTCGGGAGAAGA |
| | AAAGAGAAATAACAG | CCCGGAGTACTTCAG | GGCTCGGGAGAAGAT |
| 10 | AAGAGAAATAACAGC | CCGGAGTACTTCAGC | GCTCGGGAGAAGATC |
| | AGAGAAATAACAGCA | CGGAGTACTTCAGCG | CTCGGGAGAAGATCA |
| | GAGAAATAACAGCAG | GGAGTACTTCAGCGC | TCGGGAGAAGATCAC |
| | AGAAATAACAGCAGG | GAGTACTTCAGCGCT | CGGGAGAAGATCACC |
| | GAAATAACAGCAGGC | AGTACTTCAGCGCTG | GGGAGAAGATCACCA |
| 15 | AAATAACAGCAGGCT | GTACTTCAGCGCTGC | GGAGAAGATCACCAT |
| | AATAACAGCAGGCTG | TACTTCAGCGCTGCT | GAGAAGATCACCATG |
| | ATAACAGCAGGCTGG | ACTTCAGCGCTGCTG | AGAAGATCACCATGA |
| | TAACAGCAGGCTGGG | CTTCAGCGCTGCTGA | GAAGATCACCATGAG |
| | AACAGCAGGCTGGGG | TTCAGCGCTGCTGAT | AAGATCACCATGAGC |
| 20 | ACAGCAGGCTGGGGA | TCAGCGCTGCTGATG | AGATCACCATGAGCC |
| | CAGCAGGCTGGGGAA | CAGCGCTGCTGATGT | GATCACCATGAGCCG |
| | AGCAGGCTGGGGAAT | AGCGCTGCTGATGTG | ATCACCATGAGCCGG |
| | GCAGGCTGGGGAATG | GCGCTGCTGATGTGT | TCACCATGAGCCGGG |
| | CAGGCTGGGGAATGG | CGCTGCTGATGTGTA | CACCATGAGCCGGGA |
| 25 | AGGCTGGGGAATGGA | GCTGCTGATGTGTAC | ACCATGAGCCGGGAA |
| | GGCTGGGGAATGGAG | CTGCTGATGTGTACG | CCATGAGCCGGGAAC |
| | GCTGGGGAATGGAGT | TGCTGATGTGTACGT | CATGAGCCGGGAACT |
| | CTGGGGAATGGAGTG | GCTGATGTGTACGTT | ATGAGCCGGGAACTT |
| | TGGGGAATGGAGTGC | CTGATGTGTACGTTC | TGAGCCGGGAACTTG |
| 30 | GGGGAATGGAGTGCT | TGATGTGTACGTTCC | GAGCCGGGAACTTGG |
| | GGGAATGGAGTGCTG | GATGTGTACGTTCCT | AGCCGGGAACTTGGG |
| | GGAATGGAGTGCTGT | ATGTGTACGTTCCTG | GCCGGGAACTTGGGC |
| | GAATGGAGTGCTGTA | TGTGTACGTTCCTGA | CCGGGAACTTGGGCA |
| | AATGGAGTGCTGTAT | GTGTACGTTCCTGAT | CGGGAACTTGGGCAG |
| 35 | ATGGAGTGCTGTATG | TGTACGTTCCTGATG | GGGAACTTGGGCAGG |
| | TGGAGTGCTGTATGC | GTACGTTCCTGATGA | GGAACTTGGGCAGGG |
| | GGAGTGCTGTATGCC | TACGTTCCTGATGAG | GAACTTGGGCAGGGG |
| | GAGTGCTGTATGCCT | ACGTTCCTGATGAGT | AACTTGGGCAGGGGT |
| | AGTGCTGTATGCCTC | CGTTCCTGATGAGTG | ACTTGGGCAGGGGTC |
| 40 | GTGCTGTATGCCTCT | GTTCCTGATGAGTGG | CTTGGGCAGGGGTCG |
| | TGCTGTATGCCTCTG | TTCCTGATGAGTGGG | TTGGGCAGGGGTCGT |
| | GCTGTATGCCTCTGT | TCCTGATGAGTGGGA | TGGGCAGGGGTCGTT |
| | CTGTATGCCTCTGTG | CCTGATGAGTGGGAG | GGGCAGGGGTCGTTT |
| | TGTATGCCTCTGTGA | CTGATGAGTGGGAGG | GGCAGGGGTCGTTTG |
| 45 | GTATGCCTCTGTGAA | TGATGAGTGGGAGGT | GCAGGGGTCGTTTGG |
| | TATGCCTCTGTGAAC | GATGAGTGGGAGGTG | CAGGGGTCGTTTGGG |
| | ATGCCTCTGTGAACC | ATGAGTGGGAGGTGG | AGGGGTCGTTTGGGA |
| | TGCCTCTGTGAACCC | TGAGTGGGAGGTGGC | GGGGTCGTTTGGGAT |
| | GCCTCTGTGAACCCG | GAGTGGGAGGTGGCT | GGGTCGTTTGGGATG |
| 50 | CCTCTGTGAACCCGG | AGTGGGAGGTGGCTC | GGTCGTTTGGGATGG |
| | CTCTGTGAACCCGGA | GTGGGAGGTGGCTCG | GTCGTTTGGGATGGT |

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|---|---|---|---|
| | TCGTTTGGGATGGTC | CCTGAAACCAGAGTG | GAGAGGATTGAGTTT |
| | CGTTTGGGATGGTCT | CTGAAACCAGAGTGG | AGAGGATTGAGTTTC |
| | GTTTGGGATGGTCTA | TGAAACCAGAGTGGC | GAGGATTGAGTTTCT |
| | TTTGGGATGGTCTAT | GAAACCAGAGTGGCC | AGGATTGAGTTTCTC |
| 5 | TTGGGATGGTCTATG | AAACCAGAGTGGCCA | GGATTGAGTTTCTCA |
| | TGGGATGGTCTATGA | AACCAGAGTGGCCAT | GATTGAGTTTCTCAA |
| | GGGATGGTCTATGAA | ACCAGAGTGGCCATT | ATTGAGTTTCTCAAC |
| | GGATGGTCTATGAAG | CCAGAGTGGCCATTA | TTGAGTTTCTCAACG |
| | GATGGTCTATGAAGG | CAGAGTGGCCATTAA | TGAGTTTCTCAACGA |
| 10 | ATGGTCTATGAAGGA | AGAGTGGCCATTAAA | GAGTTTCTCAACGAA |
| | TGGTCTATGAAGGAG | GAGTGGCCATTAAAA | AGTTTCTCAACGAAG |
| | GGTCTATGAAGGAGT | AGTGGCCATTAAAAC | GTTTCTCAACGAAGC |
| | GTCTATGAAGGAGTT | GTGGCCATTAAAACA | TTTCTCAACGAAGCT |
| | TCTATGAAGGAGTTG | TGGCCATTAAAACAG | TTCTCAACGAAGCTT |
| 15 | CTATGAAGGAGTTGC | GGCCATTAAAACAGT | TCTCAACGAAGCTTC |
| | TATGAAGGAGTTGCC | GCCATTAAAACAGTG | CTCAACGAAGCTTCT |
| | ATGAAGGAGTTGCCA | CCATTAAAACAGTGA | TCAACGAAGCTTCTG |
| | TGAAGGAGTTGCCAA | CATTAAAACAGTGAA | CAACGAAGCTTCTGT |
| | GAAGGAGTTGCCAAG | ATTAAAACAGTGAAC | AACGAAGCTTCTGTG |
| 20 | AAGGAGTTGCCAAGG | TTAAAACAGTGAACG | ACGAAGCTTCTGTGA |
| | AGGAGTTGCCAAGGG | TAAAACAGTGAACGA | CGAAGCTTCTGTGAT |
| | GGAGTTGCCAAGGGT | AAAACAGTGAACGAG | GAAGCTTCTGTGATG |
| | GAGTTGCCAAGGGTG | AAACAGTGAACGAGG | AAGCTTCTGTGATGA |
| | AGTTGCCAAGGGTGT | AACAGTGAACGAGGC | AGCTTCTGTGATGAA |
| 25 | GTTGCCAAGGGTGTG | ACAGTGAACGAGGCC | GCTTCTGTGATGAAG |
| | TTGCCAAGGGTGTGG | CAGTGAACGAGGCCG | CTTCTGTGATGAAGG |
| | TGCCAAGGGTGTGGT | AGTGAACGAGGCCGC | TTCTGTGATGAAGGA |
| | GCCAAGGGTGTGGTG | GTGAACGAGGCCGCA | TCTGTGATGAAGGAG |
| | CCAAGGGTGTGGTGA | TGAACGAGGCCGCAA | CTGTGATGAAGGAGT |
| 30 | CAAGGGTGTGGTGAA | GAACGAGGCCGCAAG | TGTGATGAAGGAGTT |
| | AAGGGTGTGGTGAAA | AACGAGGCCGCAAGC | GTGATGAAGGAGTTC |
| | AGGGTGTGGTGAAAG | ACGAGGCCGCAAGCA | TGATGAAGGAGTTCA |
| | GGGTGTGGTGAAAGA | CGAGGCCGCAAGCAT | GATGAAGGAGTTCAA |
| | GGTGTGGTGAAAGAT | GAGGCCGCAAGCATG | ATGAAGGAGTTCAAT |
| 35 | GTGTGGTGAAAGATG | AGGCCGCAAGCATGC | TGAAGGAGTTCAATT |
| | TGTGGTGAAAGATGA | GGCCGCAAGCATGCG | GAAGGAGTTCAATTG |
| | GTGGTGAAAGATGAA | GCCGCAAGCATGCGT | AAGGAGTTCAATTGT |
| | TGGTGAAAGATGAAC | CCGCAAGCATGCGTG | AGGAGTTCAATTGTC |
| | GGTGAAAGATGAACC | CGCAAGCATGCGTGA | GGAGTTCAATTGTCA |
| 40 | GTGAAAGATGAACCT | GCAAGCATGCGTGAG | GAGTTCAATTGTCAC |
| | TGAAAGATGAACCTG | CAAGCATGCGTGAGA | AGTTCAATTGTCACC |
| | GAAAGATGAACCTGA | AAGCATGCGTGAGAG | GTTCAATTGTCACCA |
| | AAAGATGAACCTGAA | AGCATGCGTGAGAGG | TTCAATTGTCACCAT |
| | AAGATGAACCTGAAA | GCATGCGTGAGAGGA | TCAATTGTCACCATG |
| 45 | AGATGAACCTGAAAC | CATGCGTGAGAGGAT | CAATTGTCACCATGT |
| | GATGAACCTGAAACC | ATGCGTGAGAGGATT | AATTGTCACCATGTG |
| | ATGAACCTGAAACCA | TGCGTGAGAGGATTG | ATTGTCACCATGTGG |
| | TGAACCTGAAACCAG | GCGTGAGAGGATTGA | TTGTCACCATGTGGT |
| | GAACCTGAAACCAGA | CGTGAGAGGATTGAG | TGTCACCATGTGGTG |
| 50 | AACCTGAAACCAGAG | GTGAGAGGATTGAGT | GTCACCATGTGGTGC |
| | ACCTGAAACCAGAGT | TGAGAGGATTGAGTT | TCACCATGTGGTGCG |

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|---|---|---|---|
| | CACCATGTGGTGCGA | GTCATCATGGAACTG | CTGAGGCCAGAAATG |
| | ACCATGTGGTGCGAT | TCATCATGGAACTGA | TGAGGCCAGAAATGG |
| | CCATGTGGTGCGATT | CATCATGGAACTGAT | GAGGCCAGAAATGGA |
| | CATGTGGTGCGATTG | ATCATGGAACTGATG | AGGCCAGAAATGGAG |
| 5 | ATGTGGTGCGATTGC | TCATGGAACTGATGA | GGCCAGAAATGGAGA |
| | TGTGGTGCGATTGCT | CATGGAACTGATGAC | GCCAGAAATGGAGAA |
| | GTGGTGCGATTGCTG | ATGGAACTGATGACA | CCAGAAATGGAGAAT |
| | TGGTGCGATTGCTGG | TGGAACTGATGACAC | CAGAAATGGAGAATA |
| | GGTGCGATTGCTGGG | GGAACTGATGACACG | AGAAATGGAGAATAA |
| 10 | GTGCGATTGCTGGGT | GAACTGATGACACGG | GAAATGGAGAATAAT |
| | TGCGATTGCTGGGTG | AACTGATGACACGGG | AAATGGAGAATAATC |
| | GCGATTGCTGGGTGT | ACTGATGACACGGGG | AATGGAGAATAATCC |
| | CGATTGCTGGGTGTG | CTGATGACACGGGGC | ATGGAGAATAATCCA |
| | GATTGCTGGGTGTGG | TGATGACACGGGGCG | TGGAGAATAATCCAG |
| 15 | ATTGCTGGGTGTGGT | GATGACACGGGGCGA | GGAGAATAATCCAGT |
| | TTGCTGGGTGTGGTG | ATGACACGGGGCGAT | GAGAATAATCCAGTC |
| | TGCTGGGTGTGGTGT | TGACACGGGGCGATC | AGAATAATCCAGTCC |
| | GCTGGGTGTGGTGTC | GACACGGGGCGATCT | GAATAATCCAGTCCT |
| | CTGGGTGTGGTGTCC | ACACGGGGCGATCTC | AATAATCCAGTCCTA |
| 20 | TGGGTGTGGTGTCCC | CACGGGGCGATCTCA | ATAATCCAGTCCTAG |
| | GGGTGTGGTGTCCCA | ACGGGGCGATCTCAA | TAATCCAGTCCTAGC |
| | GGTGTGGTGTCCCAA | CGGGGCGATCTCAAA | AATCCAGTCCTAGCA |
| | GTGTGGTGTCCCAAG | GGGGCGATCTCAAAA | ATCCAGTCCTAGCAC |
| | TGTGGTGTCCCAAGG | GGGCGATCTCAAAAG | TCCAGTCCTAGCACC |
| 25 | GTGGTGTCCCAAGGC | GGCGATCTCAAAAGT | CCAGTCCTAGCACCT |
| | TGGTGTCCCAAGGCC | GCGATCTCAAAAGTT | CAGTCCTAGCACCTC |
| | GGTGTCCCAAGGCCA | CGATCTCAAAAGTTA | AGTCCTAGCACCTCC |
| | GTGTCCCAAGGCCAG | GATCTCAAAAGTTAT | GTCCTAGCACCTCCA |
| | TGTCCCAAGGCCAGC | ATCTCAAAAGTTATC | TCCTAGCACCTCCAA |
| 30 | GTCCCAAGGCCAGCC | TCTCAAAAGTTATCT | CCTAGCACCTCCAAG |
| | TCCCAAGGCCAGCCA | CTCAAAAGTTATCTC | CTAGCACCTCCAAGC |
| | CCCAAGGCCAGCCAA | TCAAAAGTTATCTCC | TAGCACCTCCAAGCC |
| | CCAAGGCCAGCCAAC | CAAAAGTTATCTCCG | AGCACCTCCAAGCCT |
| | CAAGGCCAGCCAACA | AAAAGTTATCTCCGG | GCACCTCCAAGCCTG |
| 35 | AAGGCCAGCCAACAC | AAAGTTATCTCCGGT | CACCTCCAAGCCTGA |
| | AGGCCAGCCAACACT | AAGTTATCTCCGGTC | ACCTCCAAGCCTGAG |
| | GGCCAGCCAACACTG | AGTTATCTCCGGTCT | CCTCCAAGCCTGAGC |
| | GCCAGCCAACACTGG | GTTATCTCCGGTCTC | CTCCAAGCCTGAGCA |
| | CCAGCCAACACTGGT | TTATCTCCGGTCTCT | TCCAAGCCTGAGCAA |
| 40 | CAGCCAACACTGGTC | TATCTCCGGTCTCTG | CCAAGCCTGAGCAAG |
| | AGCCAACACTGGTCA | ATCTCCGGTCTCTGA | CAAGCCTGAGCAAGA |
| | GCCAACACTGGTCAT | TCTCCGGTCTCTGAG | AAGCCTGAGCAAGAT |
| | CCAACACTGGTCATC | CTCCGGTCTCTGAGG | AGCCTGAGCAAGATG |
| | CAACACTGGTCATCA | TCCGGTCTCTGAGGC | GCCTGAGCAAGATGA |
| 45 | AACACTGGTCATCAT | CCGGTCTCTGAGGCC | CCTGAGCAAGATGAT |
| | ACACTGGTCATCATG | CGGTCTCTGAGGCCA | CTGAGCAAGATGATT |
| | CACTGGTCATCATGG | GGTCTCTGAGGCCAG | TGAGCAAGATGATTC |
| | ACTGGTCATCATGGA | GTCTCTGAGGCCAGA | GAGCAAGATGATTCA |
| | CTGGTCATCATGGAA | TCTCTGAGGCCAGAA | AGCAAGATGATTCAG |
| 50 | TGGTCATCATGGAAC | CTCTGAGGCCAGAAA | GCAAGATGATTCAGA |
| | GGTCATCATGGAACT | TCTGAGGCCAGAAAT | CAAGATGATTCAGAT |

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|---|---|---|---|
| | AAGATGATTCAGATG | GCCAATAAGTTCGTC | GAAGATTTCACAGTC |
| | AGATGATTCAGATGG | CCAATAAGTTCGTCC | AAGATTTCACAGTCA |
| | GATGATTCAGATGGC | CAATAAGTTCGTCCA | AGATTTCACAGTCAA |
| | ATGATTCAGATGGCC | AATAAGTTCGTCCAC | GATTTCACAGTCAAA |
| 5 | TGATTCAGATGGCCG | ATAAGTTCGTCCACA | ATTTCACAGTCAAAA |
| | GATTCAGATGGCCGG | TAAGTTCGTCCACAG | TTTCACAGTCAAAAT |
| | ATTCAGATGGCCGGA | AAGTTCGTCCACAGA | TTCACAGTCAAAATC |
| | TTCAGATGGCCGGAG | AGTTCGTCCACAGAG | TCACAGTCAAAATCG |
| | TCAGATGGCCGGAGA | GTTCGTCCACAGAGA | CACAGTCAAAATCGG |
| 10 | CAGATGGCCGGAGAG | TTCGTCCACAGAGAC | ACAGTCAAAATCGGA |
| | AGATGGCCGGAGAGA | TCGTCCACAGAGACC | CAGTCAAAATCGGAG |
| | GATGGCCGGAGAGAT | CGTCCACAGAGACCT | AGTCAAAATCGGAGA |
| | ATGGCCGGAGAGATT | GTCCACAGAGACCTT | GTCAAAATCGGAGAT |
| | TGGCCGGAGAGATTG | TCCACAGAGACCTTG | TCAAAATCGGAGATT |
| 15 | GGCCGGAGAGATTGC | CCACAGAGACCTTGC | CAAAATCGGAGATTT |
| | GCCGGAGAGATTGCA | CACAGAGACCTTGCT | AAAATCGGAGATTTT |
| | CCGGAGAGATTGCAG | ACAGAGACCTTGCTG | AAATCGGAGATTTTG |
| | CGGAGAGATTGCAGA | CAGAGACCTTGCTGC | AATCGGAGATTTTGG |
| | GGAGAGATTGCAGAC | AGAGACCTTGCTGCC | ATCGGAGATTTTGGT |
| 20 | GAGAGATTGCAGACG | GAGACCTTGCTGCCC | TCGGAGATTTTGGTA |
| | AGAGATTGCAGACGG | AGACCTTGCTGCCCG | CGGAGATTTTGGTAT |
| | GAGATTGCAGACGGC | GACCTTGCTGCCCGG | GGAGATTTTGGTATG |
| | AGATTGCAGACGGCA | ACCTTGCTGCCCGGA | GAGATTTTGGTATGA |
| | GATTGCAGACGGCAT | CCTTGCTGCCCGGAA | AGATTTTGGTATGAC |
| 25 | ATTGCAGACGGCATG | CTTGCTGCCCGGAAT | GATTTTGGTATGACG |
| | TTGCAGACGGCATGG | TTGCTGCCCGGAATT | ATTTTGGTATGACGC |
| | TGCAGACGGCATGGC | TGCTGCCCGGAATTG | TTTTGGTATGACGCG |
| | GCAGACGGCATGGCA | GCTGCCCGGAATTGC | TTTGGTATGACGCGA |
| | CAGACGGCATGGCAT | CTGCCCGGAATTGCA | TTGGTATGACGCGAG |
| 30 | AGACGGCATGGCATA | TGCCCGGAATTGCAT | TGGTATGACGCGAGA |
| | GACGGCATGGCATAC | GCCCGGAATTGCATG | GGTATGACGCGAGAT |
| | ACGGCATGGCATACC | CCCGGAATTGCATGG | GTATGACGCGAGATA |
| | CGGCATGGCATACCT | CCGGAATTGCATGGT | TATGACGCGAGATAT |
| | GGCATGGCATACCTC | CGGAATTGCATGGTA | ATGACGCGAGATATC |
| 35 | GCATGGCATACCTCA | GGAATTGCATGGTAG | TGACGCGAGATATCT |
| | CATGGCATACCTCAA | GAATTGCATGGTAGC | GACGCGAGATATCTA |
| | ATGGCATACCTCAAC | AATTGCATGGTAGCC | ACGCGAGATATCTAT |
| | TGGCATACCTCAACG | ATTGCATGGTAGCCG | CGCGAGATATCTATG |
| | GGCATACCTCAACGC | TTGCATGGTAGCCGA | GCGAGATATCTATGA |
| 40 | GCATACCTCAACGCC | TGCATGGTAGCCGAA | CGAGATATCTATGAG |
| | CATACCTCAACGCCA | GCATGGTAGCCGAAG | GAGATATCTATGAGA |
| | ATACCTCAACGCCAA | CATGGTAGCCGAAGA | AGATATCTATGAGAC |
| | TACCTCAACGCCAAT | ATGGTAGCCGAAGAT | GATATCTATGAGACA |
| | ACCTCAACGCCAATA | TGGTAGCCGAAGATT | ATATCTATGAGACAG |
| 45 | CCTCAACGCCAATAA | GGTAGCCGAAGATTT | TATCTATGAGACAGA |
| | CTCAACGCCAATAAG | GTAGCCGAAGATTTC | ATCTATGAGACAGAC |
| | TCAACGCCAATAAGT | TAGCCGAAGATTTCA | TCTATGAGACAGACT |
| | CAACGCCAATAAGTT | AGCCGAAGATTTCAC | CTATGAGACAGACTA |
| | AACGCCAATAAGTTC | GCCGAAGATTTCACA | TATGAGACAGACTAT |
| 50 | ACGCCAATAAGTTCG | CCGAAGATTTCACAG | ATGAGACAGACTATT |
| | CGCCAATAAGTTCGT | CGAAGATTTCACAGT | TGAGACAGACTATTA |

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|---|---|---|
| GAGACAGACTATTAC | ATGTCTCCTGAGTCC | TGGTCCTTCGGGGTC |
| AGACAGACTATTACC | TGTCTCCTGAGTCCC | GGTCCTTCGGGGTCG |
| GACAGACTATTACCG | GTCTCCTGAGTCCCT | GTCCTTCGGGGTCGT |
| ACAGACTATTACCGG | TCTCCTGAGTCCCTC | TCCTTCGGGGTCGTC |
| CAGACTATTACCGGA | CTCCTGAGTCCCTCA | CCTTCGGGGTCGTCC |
| AGACTATTACCGGAA | TCCTGAGTCCCTCAA | CTTCGGGGTCGTCCT |
| GACTATTACCGGAAA | CCTGAGTCCCTCAAG | TTCGGGGTCGTCCTC |
| ACTATTACCGGAAAG | CTGAGTCCCTCAAGG | TCGGGGTCGTCCTCT |
| CTATTACCGGAAAGG | TGAGTCCCTCAAGGA | CGGGGTCGTCCTCTG |
| TATTACCGGAAAGGA | GAGTCCCTCAAGGAT | GGGGTCGTCCTCTGG |
| ATTACCGGAAAGGAG | AGTCCCTCAAGGATG | GGGTCGTCCTCTGGG |
| TTACCGGAAAGGAGG | GTCCCTCAAGGATGG | GGTCGTCCTCTGGGA |
| TACCGGAAAGGAGGC | TCCCTCAAGGATGGA | GTCGTCCTCTGGGAG |
| ACCGGAAAGGAGGCA | CCCTCAAGGATGGAG | TCGTCCTCTGGGAGA |
| CCGGAAAGGAGGCAA | CCTCAAGGATGGAGT | CGTCCTCTGGGAGAT |
| CGGAAAGGAGGCAAA | CTCAAGGATGGAGTC | GTCCTCTGGGAGATC |
| GGAAAGGAGGCAAAG | TCAAGGATGGAGTCT | TCCTCTGGGAGATCG |
| GAAAGGAGGCAAAGG | CAAGGATGGAGTCTT | CCTCTGGGAGATCGC |
| AAAGGAGGCAAAGGG | AAGGATGGAGTCTTC | CTCTGGGAGATCGCC |
| AAGGAGGCAAAGGGC | AGGATGGAGTCTTCA | TCTGGGAGATCGCCA |
| AGGAGGCAAAGGGCT | GGATGGAGTCTTCAC | CTGGGAGATCGCCAC |
| GGAGGCAAAGGGCTG | GATGGAGTCTTCACC | TGGGAGATCGCCACA |
| GAGGCAAAGGGCTGC | ATGGAGTCTTCACCA | GGGAGATCGCCACAC |
| AGGCAAAGGGCTGCT | TGGAGTCTTCACCAC | GGAGATCGCCACACT |
| GGCAAAGGGCTGCTG | GGAGTCTTCACCACT | GAGATCGCCACACTG |
| GCAAAGGGCTGCTGC | GAGTCTTCACCACTT | AGATCGCCACACTGG |
| CAAAGGGCTGCTGCC | AGTCTTCACCACTTA | GATCGCCACACTGGC |
| AAAGGGCTGCTGCCC | GTCTTCACCACTTAC | ATCGCCACACTGGCC |
| AAGGGCTGCTGCCCG | TCTTCACCACTTACT | TCGCCACACTGGCCG |
| AGGGCTGCTGCCCGT | CTTCACCACTTACTC | CGCCACACTGGCCGA |
| GGGCTGCTGCCCGTG | TTCACCACTTACTCG | GCCACACTGGCCGAG |
| GGCTGCTGCCCGTGC | TCACCACTTACTCGG | CCACACTGGCCGAGC |
| GCTGCTGCCCGTGCG | CACCACTTACTCGGA | CACACTGGCCGAGCA |
| CTGCTGCCCGTGCGC | ACCACTTACTCGGAC | ACACTGGCCGAGCAG |
| TGCTGCCCGTGCGCT | CCACTTACTCGGACG | CACTGGCCGAGCAGC |
| GCTGCCCGTGCGCTG | CACTTACTCGGACGT | ACTGGCCGAGCAGCC |
| CTGCCCGTGCGCTGG | ACTTACTCGGACGTC | CTGGCCGAGCAGCCC |
| TGCCCGTGCGCTGGA | CTTACTCGGACGTCT | TGGCCGAGCAGCCCT |
| GCCCGTGCGCTGGAT | TTACTCGGACGTCTG | GGCCGAGCAGCCCTA |
| CCCGTGCGCTGGATG | TACTCGGACGTCTGG | GCCGAGCAGCCCTAC |
| CCGTGCGCTGGATGT | ACTCGGACGTCTGGT | CCGAGCAGCCCTACC |
| CGTGCGCTGGATGTC | CTCGGACGTCTGGTC | CGAGCAGCCCTACCA |
| GTGCGCTGGATGTCT | TCGGACGTCTGGTCC | GAGCAGCCCTACCAG |
| TGCGCTGGATGTCTC | CGGACGTCTGGTCCT | AGCAGCCCTACCAGG |
| GCGCTGGATGTCTCC | GGACGTCTGGTCCTT | GCAGCCCTACCAGGG |
| CGCTGGATGTCTCCT | GACGTCTGGTCCTTC | CAGCCCTACCAGGGC |
| GCTGGATGTCTCCTG | ACGTCTGGTCCTTCG | AGCCCTACCAGGGCT |
| CTGGATGTCTCCTGA | CGTCTGGTCCTTCGG | GCCCTACCAGGGCTT |
| TGGATGTCTCCTGAG | GTCTGGTCCTTCGGG | CCCTACCAGGGCTTG |
| GGATGTCTCCTGAGT | TCTGGTCCTTCGGGG | CCTACCAGGGCTTGT |
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|---|---|---|---|
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| | CCAGGGCTTGTCCAA | TCTGGACAAGCCAGA | GTGCTGGCAGTATAA |
| | CAGGGCTTGTCCAAC | CTGGACAAGCCAGAC | TGCTGGCAGTATAAC |
| 5 | AGGGCTTGTCCAACG | TGGACAAGCCAGACA | GCTGGCAGTATAACC |
| | GGGCTTGTCCAACGA | GGACAAGCCAGACAA | CTGGCAGTATAACCC |
| | GGCTTGTCCAACGAG | GACAAGCCAGACAAC | TGGCAGTATAACCCC |
| | GCTTGTCCAACGAGC | ACAAGCCAGACAACT | GGCAGTATAACCCCA |
| | CTTGTCCAACGAGCA | CAAGCCAGACAACTG | GCAGTATAACCCCAA |
| 10 | TTGTCCAACGAGCAA | AAGCCAGACAACTGT | CAGTATAACCCCAAG |
| | TGTCCAACGAGCAAG | AGCCAGACAACTGTC | AGTATAACCCCAAGA |
| | GTCCAACGAGCAAGT | GCCAGACAACTGTCC | GTATAACCCCAAGAT |
| | TCCAACGAGCAAGTC | CCAGACAACTGTCCT | TATAACCCCAAGATG |
| | CCAACGAGCAAGTCC | CAGACAACTGTCCTG | ATAACCCCAAGATGA |
| 15 | CAACGAGCAAGTCCT | AGACAACTGTCCTGA | TAACCCCAAGATGAG |
| | AACGAGCAAGTCCTT | GACAACTGTCCTGAC | AACCCCAAGATGAGG |
| | ACGAGCAAGTCCTTC | ACAACTGTCCTGACA | ACCCCAAGATGAGGC |
| | CGAGCAAGTCCTTCG | CAACTGTCCTGACAT | CCCCAAGATGAGGCC |
| | GAGCAAGTCCTTCGC | AACTGTCCTGACATG | CCCAAGATGAGGCCT |
| 20 | AGCAAGTCCTTCGCT | ACTGTCCTGACATGC | CCAAGATGAGGCCTT |
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| | CAAGTCCTTCGCTTC | TGTCCTGACATGCTG | AAGATGAGGCCTTCC |
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| | AGTCCTTCGCTTCGT | TCCTGACATGCTGTT | GATGAGGCCTTCCTT |
| 25 | GTCCTTCGCTTCGTC | CCTGACATGCTGTTT | ATGAGGCCTTCCTTC |
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| 30 | TCGCTTCGTCATGGA | CATGCTGTTTGAACT | GCCTTCCTTCCTGGA |
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| 35 | TCGTCATGGAGGGCG | TGTTTGAACTGATGC | CCTTCCTGGAGATCA |
| | CGTCATGGAGGGCGG | GTTTGAACTGATGCG | CTTCCTGGAGATCAT |
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| 40 | ATGGAGGGCGGCCTT | GAACTGATGCGCATG | CTGGAGATCATCAGC |
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| | GGAGGGCGGCCTTCT | ACTGATGCGCATGTG | GGAGATCATCAGCAG |
| | GAGGGCGGCCTTCTG | CTGATGCGCATGTGC | GAGATCATCAGCAGC |
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| 45 | GGGCGGCCTTCTGGA | GATGCGCATGTGCTG | GATCATCAGCAGCAT |
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| | AGCATCAAAGAGGAG | AGCGAGGAGAACAAG | AACATGGAGAGCGTC |
| 5 | GCATCAAAGAGGAGA | GCGAGGAGAACAAGC | ACATGGAGAGCGTCC |
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| | ATCAAAGAGGAGATG | GAGGAGAACAAGCTG | ATGGAGAGCGTCCCC |
| | TCAAAGAGGAGATGG | AGGAGAACAAGCTGC | TGGAGAGCGTCCCCC |
| | CAAAGAGGAGATGGA | GGAGAACAAGCTGCC | GGAGAGCGTCCCCCT |
| 10 | AAAGAGGAGATGGAG | GAGAACAAGCTGCCC | GAGAGCGTCCCCCTG |
| | AAGAGGAGATGGAGC | AGAACAAGCTGCCCG | AGAGCGTCCCCCTGG |
| | AGAGGAGATGGAGCC | GAACAAGCTGCCCGA | GAGCGTCCCCCTGGA |
| | GAGGAGATGGAGCCT | AACAAGCTGCCCGAG | AGCGTCCCCCTGGAC |
| | AGGAGATGGAGCCTG | ACAAGCTGCCCGAGC | GCGTCCCCCTGGACC |
| 15 | GGAGATGGAGCCTGG | CAAGCTGCCCGAGCC | CGTCCCCCTGGACCC |
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| | AGATGGAGCCTGGCT | AGCTGCCCGAGCCGG | TCCCCCTGGACCCCT |
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| | ATGGAGCCTGGCTTC | CTGCCCGAGCCGGAG | CCCCTGGACCCCTCG |
| 20 | TGGAGCCTGGCTTCC | TGCCCGAGCCGGAGG | CCCTGGACCCCTCGG |
| | GGAGCCTGGCTTCCG | GCCCGAGCCGGAGGA | CCTGGACCCCTCGGC |
| | GAGCCTGGCTTCCGG | CCCGAGCCGGAGGAG | CTGGACCCCTCGGCC |
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| 30 | CTTCCGGGAGGTCTC | GGAGGAGCTGGACCT | CTCGGCCTCCTCGTC |
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| | CGGGAGGTCTCCTTC | GAGCTGGACCTGGAG | GCCTCCTCGTCCTCC |
| 35 | GGGAGGTCTCCTTCT | AGCTGGACCTGGAGC | CCTCCTCGTCCTCCC |
| | GGAGGTCTCCTTCTA | GCTGGACCTGGAGCC | CTCCTCGTCCTCCCT |
| | GAGGTCTCCTTCTAC | CTGGACCTGGAGCCA | TCCTCGTCCTCCCTG |
| | AGGTCTCCTTCTACT | TGGACCTGGAGCCAG | CCTCGTCCTCCCTGC |
| | GGTCTCCTTCTACTA | GGACCTGGAGCCAGA | CTCGTCCTCCCTGCC |
| 40 | GTCTCCTTCTACTAC | GACCTGGAGCCAGAG | TCGTCCTCCCTGCCA |
| | TCTCCTTCTACTACA | ACCTGGAGCCAGAGA | CGTCCTCCCTGCCAC |
| | CTCCTTCTACTACAG | CCTGGAGCCAGAGAA | GTCCTCCCTGCCACT |
| | TCCTTCTACTACAGC | CTGGAGCCAGAGAAC | TCCTCCCTGCCACTG |
| | CCTTCTACTACAGCG | TGGAGCCAGAGAACA | CCTCCCTGCCACTGC |
| 45 | CTTCTACTACAGCGA | GGAGCCAGAGAACAT | CTCCCTGCCACTGCC |
| | TTCTACTACAGCGAG | GAGCCAGAGAACATG | TCCCTGCCACTGCCC |
| | TCTACTACAGCGAGG | AGCCAGAGAACATGG | CCCTGCCACTGCCCG |
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| | TACTACAGCGAGGAG | CCAGAGAACATGGAG | CTGCCACTGCCCGAC |
| 50 | ACTACAGCGAGGAGA | CAGAGAACATGGAGA | TGCCACTGCCCGACA |
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|---|---|---|
| CCACTGCCCGACAGA | GGGGTGCTGGTCCTC | ATGAACGGGGGCCGC |
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| ACTGCCCGACAGACA | GGTGCTGGTCCTCCG | GAACGGGGGCCGCAA |
| CTGCCCGACAGACAC | GTGCTGGTCCTCCGC | AACGGGGGCCGCAAG |
| TGCCCGACAGACACT | TGCTGGTCCTCCGCG | ACGGGGGCCGCAAGA |
| GCCCGACAGACACTC | GCTGGTCCTCCGCGC | CGGGGGCCGCAAGAA |
| CCCGACAGACACTCA | CTGGTCCTCCGCGCC | GGGGGCCGCAAGAAC |
| CCGACAGACACTCAG | TGGTCCTCCGCGCCA | GGGGCCGCAAGAACG |
| CGACAGACACTCAGG | GGTCCTCCGCGCCAG | GGGCCGCAAGAACGA |
| GACAGACACTCAGGA | GTCCTCCGCGCCAGC | GGCCGCAAGAACGAG |
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| CAGACACTCAGGACA | CCTCCGCGCCAGCTT | CCGCAAGAACGAGCG |
| AGACACTCAGGACAC | CTCCGCGCCAGCTTC | CGCAAGAACGAGCGG |
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| GGACACAAGGCCGAG | AGCTTCGACGAGAGA | GAGCGGGCCTTGCCG |
| GACACAAGGCCGAGA | GCTTCGACGAGAGAC | AGCGGGCCTTGCCGC |
| ACACAAGGCCGAGAA | CTTCGACGAGAGACA | GCGGGCCTTGCCGCT |
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| ACAAGGCCGAGAACG | TCGACGAGAGACAGC | GGGCCTTGCCGCTGC |
| CAAGGCCGAGAACGG | CGACGAGAGACAGCC | GGCCTTGCCGCTGCC |
| AAGGCCGAGAACGGC | GACGAGAGACAGCCT | GCCTTGCCGCTGCCC |
| AGGCCGAGAACGGCC | ACGAGAGACAGCCTT | CCTTGCCGCTGCCCC |
| GGCCGAGAACGGCCC | CGAGAGACAGCCTTA | CTTGCCGCTGCCCCA |
| GCCGAGAACGGCCCC | GAGAGACAGCCTTAC | TTGCCGCTGCCCCAG |
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| AGAACGGCCCCGGCC | GACAGCCTTACGCCC | CGCTGCCCCAGTCTT |
| GAACGGCCCCGGCCC | ACAGCCTTACGCCCA | GCTGCCCCAGTCTTC |
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| GGCCCTGGGGTGCTG | GCCCACATGAACGGG | TCTTCGACCTGCTGA |
| GCCCTGGGGTGCTGG | CCCACATGAACGGGG | CTTCGACCTGCTGAT |
| CCCTGGGGTGCTGGT | CCACATGAACGGGGG | TTCGACCTGCTGATC |
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| CTGGGGTGCTGGTCC | ACATGAACGGGGGCC | CGACCTGCTGATCCT |
| TGGGGTGCTGGTCCT | CATGAACGGGGGCCG | GACCTGCTGATCCTT |

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|---|---|---|---|
| | ACCTGCTGATCCTTG | GCGCAGCGGGGTGGG | TCCTGTACCTCAGTG |
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| 5 | GCTGATCCTTGGATC | AGCGGGGTGGGGGGG | GTACCTCAGTGGATC |
| | CTGATCCTTGGATCC | GCGGGGTGGGGGGGG | TACCTCAGTGGATCT |
| | TGATCCTTGGATCCT | CGGGGTGGGGGGGGA | ACCTCAGTGGATCTT |
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| | ATCCTTGGATCCTGA | GGGTGGGGGGGGAGA | CTCAGTGGATCTTCA |
| 10 | TCCTTGGATCCTGAA | GGTGGGGGGGGAGAG | TCAGTGGATCTTCAG |
| | CCTTGGATCCTGAAT | GTGGGGGGGGAGAGA | CAGTGGATCTTCAGT |
| | CTTGGATCCTGAATC | TGGGGGGGGAGAGAG | AGTGGATCTTCAGTT |
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| | TGGATCCTGAATCTG | GGGGGGGAGAGAGAG | TGGATCTTCAGTTCT |
| 15 | GGATCCTGAATCTGT | GGGGGGAGAGAGAGT | GGATCTTCAGTTCTG |
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| 20 | CTGAATCTGTGCAAA | GAGAGAGAGTTTTAA | TTCAGTTCTGCCCTT |
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| | AATCTGTGCAAACAG | AGAGAGTTTTAACAA | AGTTCTGCCCTTGCT |
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| 25 | TCTGTGCAAACAGTA | AGAGTTTTAACAATC | TTCTGCCCTTGCTGC |
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| | TGTGCAAACAGTAAC | AGTTTTAACAATCCA | CTGCCCTTGCTGCCC |
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| | TGCAAACAGTAACGT | TTTTAACAATCCATT | GCCCTTGCTGCCCGC |
| 30 | GCAAACAGTAACGTG | TTTAACAATCCATTC | CCCTTGCTGCCCGCG |
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| 35 | CAGTAACGTGTGCGC | CAATCCATTCACAAG | GCTGCCCGCGGGAGA |
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| | GTGCGCACGCGCAGC | CACAAGCCTCCTGTA | GGGAGACAGCTTCTC |
| 45 | TGCGCACGCGCAGCG | ACAAGCCTCCTGTAC | GGAGACAGCTTCTCT |
| | GCGCACGCGCAGCGG | CAAGCCTCCTGTACC | GAGACAGCTTCTCTG |
| | CGCACGCGCAGCGGG | AAGCCTCCTGTACCT | AGACAGCTTCTCTGC |
| | GCACGCGCAGCGGGG | AGCCTCCTGTACCTC | GACAGCTTCTCTGCA |
| | CACGCGCAGCGGGGT | GCCTCCTGTACCTCA | ACAGCTTCTCTGCAG |
| 50 | ACGCGCAGCGGGGTG | CCTCCTGTACCTCAG | CAGCTTCTCTGCAGT |
| | CGCGCAGCGGGGTGG | CTCCTGTACCTCAGT | AGCTTCTCTGCAGTA |

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| | CTTCTCTGCAGTAAA | AGCTTTTTATTCCCT | TTAATGACAACACTT |
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| | TCTCTGCAGTAAAAC | CTTTTTATTCCCTGC | AATGACAACACTTAA |
| 5 | CTCTGCAGTAAAACA | TTTTTATTCCCTGCC | ATGACAACACTTAAT |
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| | CTGCAGTAAAACACA | TTTATTCCCTGCCCA | GACAACACTTAATAG |
| | TGCAGTAAAACACAT | TTATTCCCTGCCCAA | ACAACACTTAATAGC |
| | GCAGTAAAACACATT | TATTCCCTGCCCAAA | CAACACTTAATAGCA |
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| | AGTAAAACACATTTG | TTCCCTGCCCAAACC | ACACTTAATAGCAAC |
| | GTAAAACACATTTGG | TCCCTGCCCAAACCC | CACTTAATAGCAACA |
| | TAAAACACATTTGGG | CCCTGCCCAAACCCT | ACTTAATAGCAACAG |
| | AAAACACATTTGGGA | CCTGCCCAAACCCTT | CTTAATAGCAACAGA |
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| | TTTGGGATGTTCCTT | AACCCTTAACTGACA | CAACAGAGCACTTGA |
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| 25 | GGGATGTTCCTTTTT | CCTTAACTGACATGG | CAGAGCACTTGAGAA |
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| | GATGTTCCTTTTTTC | TTAACTGACATGGGC | GAGCACTTGAGAACC |
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| 30 | GTTCCTTTTTTCAAT | ACTGACATGGGCCTT | CACTTGAGAACCAGT |
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| | TCCTTTTTTCAATAT | TGACATGGGCCTTTA | CTTGAGAACCAGTCT |
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| | CTTTTTTCAATATGC | ACATGGGCCTTTAAG | TGAGAACCAGTCTCC |
| 35 | TTTTTTCAATATGCA | CATGGGCCTTTAAGA | GAGAACCAGTCTCCT |
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| | TGCAAGCAGCTTTTT | AAGAACCTTAATGAC | TCCTCACTCTGTCCC |
| | GCAAGCAGCTTTTTA | AGAACCTTAATGACA | CCTCACTCTGTCCCT |
| | CAAGCAGCTTTTTAT | GAACCTTAATGACAA | CTCACTCTGTCCCTG |
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| 50 | AGCAGCTTTTTATTC | ACCTTAATGACAACA | CACTCTGTCCCTGTC |
| | GCAGCTTTTTATTCC | CCTTAATGACAACAC | ACTCTGTCCCTGTCC |

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|---|---|---|---|
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| | TCTGTCCCTGTCCTT | ACGGAAAAATAATTG | GAGGAAGTGGCTGTC |
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| | TGTCCCTGTCCTTCC | GGAAAAATAATTGCC | GGAAGTGGCTGTCCC |
| 5 | GTCCCTGTCCTTCCC | GAAAAATAATTGCCA | GAAGTGGCTGTCCCT |
| | TCCCTGTCCTTCCCT | AAAAATAATTGCCAC | AAGTGGCTGTCCCTG |
| | CCCTGTCCTTCCCTG | AAAATAATTGCCACA | AGTGGCTGTCCCTGT |
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| | CTGTCCTTCCCTGTT | AATAATTGCCACAAG | TGGCTGTCCCTGTGG |
| 10 | TGTCCTTCCCTGTTC | ATAATTGCCACAAGT | GGCTGTCCCTGTGGC |
| | GTCCTTCCCTGTTCT | TAATTGCCACAAGTC | GCTGTCCCTGTGGCC |
| | TCCTTCCCTGTTCTC | AATTGCCACAAGTCC | CTGTCCCTGTGGCCC |
| | CCTTCCCTGTTCTCC | ATTGCCACAAGTCCA | TGTCCCTGTGGCCCC |
| | CTTCCCTGTTCTCCC | TTGCCACAAGTCCAG | GTCCCTGTGGCCCCA |
| 15 | TTCCCTGTTCTCCCT | TGCCACAAGTCCAGC | TCCCTGTGGCCCCAT |
| | TCCCTGTTCTCCCTT | GCCACAAGTCCAGCT | CCCTGTGGCCCCATC |
| | CCCTGTTCTCCCTTT | CCACAAGTCCAGCTG | CCTGTGGCCCCATCC |
| | CCTGTTCTCCCTTTC | CACAAGTCCAGCTGG | CTGTGGCCCCATCCA |
| | CTGTTCTCCCTTTCT | ACAAGTCCAGCTGGG | TGTGGCCCCATCCAA |
| 20 | TGTTCTCCCTTTCTC | CAAGTCCAGCTGGGA | GTGGCCCCATCCAAC |
| | GTTCTCCCTTTCTCT | AAGTCCAGCTGGGAA | TGGCCCCATCCAACC |
| | TTCTCCCTTTCTCTC | AGTCCAGCTGGGAAG | GGCCCCATCCAACCA |
| | TCTCCCTTTCTCTCT | GTCCAGCTGGGAAGC | GCCCCATCCAACCAC |
| | CTCCCTTTCTCTCTC | TCCAGCTGGGAAGCC | CCCCATCCAACCACT |
| 25 | TCCCTTTCTCTCTCC | CCAGCTGGGAAGCCC | CCCATCCAACCACTG |
| | CCCTTTCTCTCTCCT | CAGCTGGGAAGCCCT | CCATCCAACCACTGT |
| | CCTTTCTCTCTCCTC | AGCTGGGAAGCCCTT | CATCCAACCACTGTA |
| | CTTTCTCTCTCCTCT | GCTGGGAAGCCCTTT | ATCCAACCACTGTAC |
| | TTTCTCTCTCCTCTC | CTGGGAAGCCCTTTT | TCCAACCACTGTACA |
| 30 | TTCTCTCTCCTCTCT | TGGGAAGCCCTTTTT | CCAACCACTGTACAC |
| | TCTCTCTCCTCTCTG | GGGAAGCCCTTTTTA | CAACCACTGTACACA |
| | CTCTCTCCTCTCTGC | GGAAGCCCTTTTTAT | AACCACTGTACACAC |
| | TCTCTCCTCTCTGCT | GAAGCCCTTTTTATC | ACCACTGTACACACC |
| | CTCTCCTCTCTGCTT | AAGCCCTTTTTATCA | CCACTGTACACACCC |
| 35 | TCTCCTCTCTGCTTC | AGCCCTTTTTATCAG | CACTGTACACACCCG |
| | CTCCTCTCTGCTTCA | GCCCTTTTTATCAGT | ACTGTACACACCCGC |
| | TCCTCTCTGCTTCAT | CCCTTTTTATCAGTT | CTGTACACACCCGCC |
| | CCTCTCTGCTTCATA | CCTTTTTATCAGTTT | TGTACACACCCGCCT |
| | CTCTCTGCTTCATAA | CTTTTTATCAGTTTG | GTACACACCCGCCTG |
| 40 | TCTCTGCTTCATAAC | TTTTTATCAGTTTGA | TACACACCCGCCTGA |
| | CTCTGCTTCATAACG | TTTTATCAGTTTGAG | ACACACCCGCCTGAC |
| | TCTGCTTCATAACGG | TTTATCAGTTTGAGG | CACACCCGCCTGACA |
| | CTGCTTCATAACGGA | TTATCAGTTTGAGGA | ACACCCGCCTGACAC |
| | TGCTTCATAACGGAA | TATCAGTTTGAGGAA | CACCCGCCTGACACC |
| 45 | GCTTCATAACGGAAA | ATCAGTTTGAGGAAG | ACCCGCCTGACACCG |
| | CTTCATAACGGAAAA | TCAGTTTGAGGAAGT | CCCGCCTGACACCGT |
| | TTCATAACGGAAAAA | CAGTTTGAGGAAGTG | CCGCCTGACACCGTG |
| | TCATAACGGAAAAAT | AGTTTGAGGAAGTGG | CGCCTGACACCGTGG |
| | CATAACGGAAAAATA | GTTTGAGGAAGTGGC | GCCTGACACCGTGGG |
| 50 | ATAACGGAAAAATAA | TTTGAGGAAGTGGCT | CCTGACACCGTGGGT |
| | TAACGGAAAAATAAT | TTGAGGAAGTGGCTG | CTGACACCGTGGGTC |

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|---|---|---|---|
| | TGACACCGTGGGTCA | TTATCTTTCACCTTT | CCAAGGCTGTTACCA |
| | GACACCGTGGGTCAT | TATCTTTCACCTTTC | CAAGGCTGTTACCAT |
| | ACACCGTGGGTCATT | ATCTTTCACCTTTCT | AAGGCTGTTACCATT |
| | CACCGTGGGTCATTA | TCTTTCACCTTTCTA | AGGCTGTTACCATTT |
| 5 | ACCGTGGGTCATTAC | CTTTCACCTTTCTAG | GGCTGTTACCATTTT |
| | CCGTGGGTCATTACA | TTTCACCTTTCTAGG | GCTGTTACCATTTTA |
| | CGTGGGTCATTACAA | TTCACCTTTCTAGGG | CTGTTACCATTTTAA |
| | GTGGGTCATTACAAA | TCACCTTTCTAGGGA | TGTTACCATTTTAAC |
| | TGGGTCATTACAAAA | CACCTTTCTAGGGAC | GTTACCATTTTAACG |
| 10 | GGGTCATTACAAAAA | ACCTTTCTAGGGACA | TTACCATTTTAACGC |
| | GGTCATTACAAAAAA | CCTTTCTAGGGACAT | TACCATTTTAACGCT |
| | GTCATTACAAAAAAA | CTTTCTAGGGACATG | ACCATTTTAACGCTG |
| | TCATTACAAAAAAAC | TTTCTAGGGACATGA | CCATTTTAACGCTGC |
| | CATTACAAAAAAACA | TTCTAGGGACATGAA | CATTTTAACGCTGCC |
| 15 | ATTACAAAAAAACAC | TCTAGGGACATGAAA | ATTTTAACGCTGCCT |
| | TTACAAAAAAACACG | CTAGGGACATGAAAT | TTTTAACGCTGCCTA |
| | TACAAAAAAACACGT | TAGGGACATGAAATT | TTTAACGCTGCCTAA |
| | ACAAAAAAACACGTG | AGGGACATGAAATTT | TTAACGCTGCCTAAT |
| | CAAAAAAACACGTGG | GGGACATGAAATTTA | TAACGCTGCCTAATT |
| 20 | AAAAAAACACGTGGA | GGACATGAAATTTAC | AACGCTGCCTAATTT |
| | AAAAAACACGTGGAG | GACATGAAATTTACA | ACGCTGCCTAATTTT |
| | AAAAACACGTGGAGA | ACATGAAATTTACAA | CGCTGCCTAATTTTG |
| | AAAACACGTGGAGAT | CATGAAATTTACAAA | GCTGCCTAATTTTGC |
| | AAACACGTGGAGATG | ATGAAATTTACAAAG | CTGCCTAATTTTGCC |
| 25 | AACACGTGGAGATGG | TGAAATTTACAAAGG | TGCCTAATTTTGCCA |
| | ACACGTGGAGATGGA | GAAATTTACAAAGGG | GCCTAATTTTGCCAA |
| | CACGTGGAGATGGAA | AAATTTACAAAGGGC | CCTAATTTTGCCAAA |
| | ACGTGGAGATGGAAA | AATTTACAAAGGGCC | CTAATTTTGCCAAAA |
| | CGTGGAGATGGAAAT | ATTTACAAAGGGCCA | TAATTTTGCCAAAAT |
| 30 | GTGGAGATGGAAATT | TTTACAAAGGGCCAT | AATTTTGCCAAAATC |
| | TGGAGATGGAAATTT | TTACAAAGGGCCATC | ATTTTGCCAAAATCC |
| | GGAGATGGAAATTTT | TACAAAGGGCCATCG | TTTTGCCAAAATCCT |
| | GAGATGGAAATTTTT | ACAAAGGGCCATCGT | TTTGCCAAAATCCTG |
| | AGATGGAAATTTTTA | CAAAGGGCCATCGTT | TTGCCAAAATCCTGA |
| 35 | GATGGAAATTTTTAC | AAAGGGCCATCGTTC | TGCCAAAATCCTGAA |
| | ATGGAAATTTTTACC | AAGGGCCATCGTTCA | GCCAAAATCCTGAAC |
| | TGGAAATTTTTACCT | AGGGCCATCGTTCAT | CCAAAATCCTGAACT |
| | GGAAATTTTTACCTT | GGGCCATCGTTCATC | CAAAATCCTGAACTT |
| | GAAATTTTTACCTTT | GGCCATCGTTCATCC | AAAATCCTGAACTTT |
| 40 | AAATTTTTACCTTTA | GCCATCGTTCATCCA | AAATCCTGAACTTTC |
| | AATTTTTACCTTTAT | CCATCGTTCATCCAA | AATCCTGAACTTTCT |
| | ATTTTTACCTTTATC | CATCGTTCATCCAAG | ATCCTGAACTTTCTC |
| | TTTTTACCTTTATCT | ATCGTTCATCCAAGG | TCCTGAACTTTCTCC |
| | TTTTACCTTTATCTT | TCGTTCATCCAAGGC | CCTGAACTTTCTCCC |
| 45 | TTTACCTTTATCTTT | CGTTCATCCAAGGCT | CTGAACTTTCTCCCT |
| | TTACCTTTATCTTTC | GTTCATCCAAGGCTG | TGAACTTTCTCCCTC |
| | TACCTTTATCTTTCA | TTCATCCAAGGCTGT | GAACTTTCTCCCTCA |
| | ACCTTTATCTTTCAC | TCATCCAAGGCTGTT | AACTTTCTCCCTCAT |
| | CCTTTATCTTTCACC | CATCCAAGGCTGTTA | ACTTTCTCCCTCATC |
| 50 | CTTTATCTTTCACCT | ATCCAAGGCTGTTAC | CTTTCTCCCTCATCG |
| | TTTATCTTTCACCTT | TCCAAGGCTGTTACC | TTTCTCCCTCATCGG |

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|---|---|---|---|
| | TTCTCCCTCATCGGC | GCATGGCAGCTGGTT | CCATCCGACTGCCCC |
| | TCTCCCTCATCGGCC | CATGGCAGCTGGTTG | CATCCGACTGCCCCT |
| | CTCCCTCATCGGCCC | ATGGCAGCTGGTTGC | ATCCGACTGCCCCTG |
| | TCCCTCATCGGCCCG | TGGCAGCTGGTTGCT | TCCGACTGCCCCTGC |
| 5 | CCCTCATCGGCCCGG | GGCAGCTGGTTGCTC | CCGACTGCCCCTGCT |
| | CCTCATCGGCCCGGC | GCAGCTGGTTGCTCC | CGACTGCCCCTGCTG |
| | CTCATCGGCCCGGCG | CAGCTGGTTGCTCCA | GACTGCCCCTGCTGT |
| | TCATCGGCCCGGCGC | AGCTGGTTGCTCCAT | ACTGCCCCTGCTGTG |
| | CATCGGCCCGGCGCT | GCTGGTTGCTCCATT | CTGCCCCTGCTGTGC |
| 10 | ATCGGCCCGGCGCTG | CTGGTTGCTCCATTT | TGCCCCTGCTGTGCT |
| | TCGGCCCGGCGCTGA | TGGTTGCTCCATTTG | GCCCCTGCTGTGCTG |
| | CGGCCCGGCGCTGAT | GGTTGCTCCATTTGA | CCCCTGCTGTGCTGC |
| | GGCCCGGCGCTGATT | GTTGCTCCATTTGAG | CCCTGCTGTGCTGCT |
| | GCCCGGCGCTGATTC | TTGCTCCATTTGAGA | CCTGCTGTGCTGCTC |
| 15 | CCCGGCGCTGATTCC | TGCTCCATTTGAGAG | CTGCTGTGCTGCTCA |
| | CCGGCGCTGATTCCT | GCTCCATTTGAGAGA | TGCTGTGCTGCTCAA |
| | CGGCGCTGATTCCTC | CTCCATTTGAGAGAC | GCTGTGCTGCTCAAG |
| | GGCGCTGATTCCTCG | TCCATTTGAGAGACA | CTGTGCTGCTCAAGG |
| | GCGCTGATTCCTCGT | CCATTTGAGAGACAC | TGTGCTGCTCAAGGC |
| 20 | CGCTGATTCCTCGTG | CATTTGAGAGACACG | GTGCTGCTCAAGGCC |
| | GCTGATTCCTCGTGT | ATTTGAGAGACACGC | TGCTGCTCAAGGCCA |
| | CTGATTCCTCGTGTC | TTTGAGAGACACGCT | GCTGCTCAAGGCCAC |
| | TGATTCCTCGTGTCC | TTGAGAGACACGCTG | CTGCTCAAGGCCACA |
| | GATTCCTCGTGTCCG | TGAGAGACACGCTGG | TGCTCAAGGCCACAG |
| 25 | ATTCCTCGTGTCCGG | GAGAGACACGCTGGC | GCTCAAGGCCACAGG |
| | TTCCTCGTGTCCGGA | AGAGACACGCTGGCG | CTCAAGGCCACAGGC |
| | TCCTCGTGTCCGGAG | GAGACACGCTGGCGA | TCAAGGCCACAGGCA |
| | CCTCGTGTCCGGAGG | AGACACGCTGGCGAC | CAAGGCCACAGGCAC |
| | CTCGTGTCCGGAGGC | GACACGCTGGCGACA | AAGGCCACAGGCACA |
| 30 | TCGTGTCCGGAGGCA | ACACGCTGGCGACAC | AGGCCACAGGCACAC |
| | CGTGTCCGGAGGCAT | CACGCTGGCGACACA | GGCCACAGGCACACA |
| | GTGTCCGGAGGCATG | ACGCTGGCGACACAC | GCCACAGGCACACAG |
| | TGTCCGGAGGCATGG | CGCTGGCGACACACT | CCACAGGCACACAGG |
| | GTCCGGAGGCATGGG | GCTGGCGACACACTC | CACAGGCACACAGGT |
| 35 | TCCGGAGGCATGGGT | CTGGCGACACACTCC | ACAGGCACACAGGTC |
| | CCGGAGGCATGGGTG | TGGCGACACACTCCG | CAGGCACACAGGTCT |
| | CGGAGGCATGGGTGA | GGCGACACACTCCGT | AGGCACACAGGTCTC |
| | GGAGGCATGGGTGAG | GCGACACACTCCGTC | GGCACACAGGTCTCA |
| | GAGGCATGGGTGAGC | CGACACACTCCGTCC | GCACACAGGTCTCAT |
| 40 | AGGCATGGGTGAGCA | GACACACTCCGTCCA | CACACAGGTCTCATT |
| | GGCATGGGTGAGCAT | ACACACTCCGTCCAT | ACACAGGTCTCATTG |
| | GCATGGGTGAGCATG | CACACTCCGTCCATC | CACAGGTCTCATTGC |
| | CATGGGTGAGCATGG | ACACTCCGTCCATCC | ACAGGTCTCATTGCT |
| | ATGGGTGAGCATGGC | CACTCCGTCCATCCG | CAGGTCTCATTGCTT |
| 45 | TGGGTGAGCATGGCA | ACTCCGTCCATCCGA | AGGTCTCATTGCTTC |
| | GGGTGAGCATGGCAG | CTCCGTCCATCCGAC | GGTCTCATTGCTTCT |
| | GGTGAGCATGGCAGC | TCCGTCCATCCGACT | GTCTCATTGCTTCTG |
| | GTGAGCATGGCAGCT | CCGTCCATCCGACTG | TCTCATTGCTTCTGA |
| | TGAGCATGGCAGCTG | CGTCCATCCGACTGC | CTCATTGCTTCTGAC |
| 50 | GAGCATGGCAGCTGG | GTCCATCCGACTGCC | TCATTGCTTCTGACT |
| | AGCATGGCAGCTGGT | TCCATCCGACTGCCC | CATTGCTTCTGACTA |

| | | |
|---|---|---|
| | ATTGCTTCTGACTAG | CTCTCAGTGAAGGTG |
| | TTGCTTCTGACTAGA | TCTCAGTGAAGGTGG |
| | TGCTTCTGACTAGAT | CTCAGTGAAGGTGGG |
| | GCTTCTGACTAGATT | TCAGTGAAGGTGGGG |
| 5 | CTTCTGACTAGATTA | CAGTGAAGGTGGGGA |
| | TTCTGACTAGATTAT | AGTGAAGGTGGGGAG |
| | TCTGACTAGATTATT | GTGAAGGTGGGGAGA |
| | CTGACTAGATTATTA | TGAAGGTGGGGAGAA |
| | TGACTAGATTATTAT | GAAGGTGGGGAGAAG |
| 10 | GACTAGATTATTATT | AAGGTGGGGAGAAGC |
| | ACTAGATTATTATTT | AGGTGGGGAGAAGCT |
| | CTAGATTATTATTTG | GGTGGGGAGAAGCTG |
| | TAGATTATTATTTGG | GTGGGGAGAAGCTGA |
| | AGATTATTATTTGGG | TGGGGAGAAGCTGAA |
| 15 | GATTATTATTTGGGG | GGGGAGAAGCTGAAC |
| | ATTATTATTTGGGGG | GGGAGAAGCTGAACC |
| | TTATTATTTGGGGGA | GGAGAAGCTGAACCG |
| | TATTATTTGGGGGAA | GAGAAGCTGAACCGG |
| | ATTATTTGGGGGAAC | AGAAGCTGAACCGGC |
| 20 | TTATTTGGGGGAACT | |
| | TATTTGGGGGAACTG | |
| | ATTTGGGGGAACTGG | |
| | TTTGGGGGAACTGGA | |
| | TTGGGGGAACTGGAC | |
| 25 | TGGGGGAACTGGACA | |
| | GGGGGAACTGGACAC | |
| | GGGGAACTGGACACA | |
| | GGGAACTGGACACAA | |
| | GGAACTGGACACAAT | |
| 30 | GAACTGGACACAATA | |
| | AACTGGACACAATAG | |
| | ACTGGACACAATAGG | |
| | CTGGACACAATAGGT | |
| | TGGACACAATAGGTC | |
| 35 | GGACACAATAGGTCT | |
| | GACACAATAGGTCTT | |
| | ACACAATAGGTCTTT | |
| | CACAATAGGTCTTTC | |
| | ACAATAGGTCTTTCT | |
| 40 | CAATAGGTCTTTCTC | |
| | AATAGGTCTTTCTCT | |
| | ATAGGTCTTTCTCTC | |
| | TAGGTCTTTCTCTCA | |
| | AGGTCTTTCTCTCAG | |
| 45 | GGTCTTTCTCTCAGT | |
| | GTCTTTCTCTCAGTG | |
| | TCTTTCTCTCAGTGA | |
| | CTTTCTCTCAGTGAA | |
| | TTTCTCTCAGTGAAG | |
| 50 | TTCTCTCAGTGAAGG | |
| | TCTCTCAGTGAAGGT | |

EXAMPLE 9

Sub-confluent HaCaT cells were treated as described above with phosphorothioate oligonucleotides IGFR.AS (antisense: 5'-ATCTCTCCGCTTCCTTTC-3'; (<400>10); ref 13) and IGFR.S (sense control: 5'-GAAAGGAAGCGGAGAGAT-3'; (<400>11); ref 13) IGF-I binding to the cell monolayers was then measured as $^{125}$I-IGF-I.

**EXAMPLE 10**

The results of this experiment are shown in Figures 7 and 8.

HaCaT cells were initially plated in DMEM with 10% v/v serum, then AS oligo experiments were performed in complete "Keratinocyte-SFM" (Gibco) to exclude the influence of exogenous IGFBPs. Oligos were synthesised as phosphorothioate (nuclease-resistant) derivatives (Bresatec, South Australia) and were as follows: antisense: AS2, 5'-GCGCCCGCTGCATGACGCCTGCAAC-3' (IGFBP-3 start codon); controls: AS2NS, 5'-CGGAGATGCCGCATGCCAGCGCAGG-3'; AS4, 5'-AGGCGGCTGACGGCACTA-3'; AS4NS, 5'-GACAGCGTCGGAGCGATC-3'; IGFRAS, 5'-ATCTCTCCGCTTCCTTTC-3';

IGFRS, 5'-GAAAGGAAGCGGAGAGAT-3'. Oligos to IGFBP-3 were based on the published sequence of Spratt *et al* [12]. AS oligos were added to HaCaT monolayers in 0.5ml medium in 24-well plates at the concentrations and addition frequencies indicated. IGFBP-3 measured in cell-conditioned medium using a dot-blot assay, adapted from the Western ligand blot method of Hossenlopp *et al* [11], in which 100$\mu$l of conditioned medium was applied to nitrocellulose filters with a vacuum dot-blot apparatus. After drying the membranes at 37°C, relative amounts of IGFBP are determined by $^{125}$I-IGF-I-binding, autoradiography and computerised imaging densitometry. Triplicate wells (except in Figure 7, where duplicate wells were measured as shown) were analysed and corrected for changes in cell number per well. Relative cell number per well was determined using an amido black dye method, developed specifically for cultured monolayers of HaCaT cells [14]. Cell numbers differed by less than 10% after treatment. For oligos to the IGF receptor, receptor quantitation in

intact HaCaT monolayers was by overnight incubation with $^{125}$I-IGF-I (30,000cpm/well) at 4°C.

## EXAMPLE 11

Experiments involving ribozymes are generally conducted as described in Internaitonal Patent Application No. WO 89/05852 and in Haselhoff and Gerlach [8]. Ribozymes are constructed with a hybridising region which is complementary in nucleotide sequence to at least part of a target RNA which, in this case, encodes IGFBP-2. Activity of ribozymes is measurable on, for example, Northern blots or using animal models such as in the nude mouse model (15; 16) or the "flaky skin" mouse model (17; 18).

## EXAMPLE 12

The methods described in Example 11 are used for the screening of ribozymes which inhibit IGFBP-3 production. The activity of the ribozymes is determined as in Example 11.

## EXAMPLE 13

The methods described in Example 11 are used for the screening of ribozymes which inhibit IGF-1 production. The activity of the ribozymes is determined as in Example 11.

## EXAMPLE 14

The methods described in Example 11 are used for the screening of ribozymes which inhibit IGF-1 production. The activity of the ribozymes is determined as in Example 11.

## EXAMPLE 15

Twenty-one antisense oligonucleotides targeted to mRNA sequences enducing the IGF-1 receptor, and four random oligonucleotides were synthesized. The antisense oligonucleotides are C5-propynyl-dU, dC 15mer phosphorothioate oligodeoxyribonucleotides. In these oligonucleotides, a phosphorothioate backbone replaces the phosphodiester backbone of naturally occurring DNA. The positions of the 21 sequence specific antisense oligonucleotides relative to the IGF-1 receptor mRNA structure are shown in Figure 9.

## EXAMPLE 16

Experiments were performed to determine the uptake of the antisense oligonucleotides of Example 15 into keratinocytes. Cells of the differentiated human keratinocyte cell line, HaCaT, were incubated for 24 hours in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% (w/v) fetal calf serum (FCS) containing fluorescently labelled oligonucleotide (R451, a randomized sequence oligonucleotide, 30nM) and cytofectin GSV (2$\mu$g/ml, Glen Research, 44901 Falcon Place, Sterling, VA 20166, Cat. No. 70-3815-78). Cells were then transferred to oligonucleotide-free medium and fluorescence microcopy and phase contrast images of the cells were obtained. Figure 10 shows fluorescence microscopy (Panel A) and phase contrast (Panel B) images of uptake of fluorescently labelled oligonucleotide in the majority of cells in a HaCaT monolayer. The degree of uptake obtained with the cationic lipid cytofectin was far greater than the uptake obtained with the next best lipid tried, Tfx-50.

A further experiment was performed to assess the uptake and toxicity associated with the use of cytofectin GSV over five days. Confluent HaCaT keratinocytes were incubated in DMEM containing fluorescently labelled oligonucleotide R451 (30nM or 100 nM) plus cytofectin GSV (2$\mu$g/ml or 5$\mu$g/ml) over 120 hours, viewed by fluorescence microscopy, tryptan blue stained, and counted. The graphs in Figure 11 depict uptake (Panel A) and toxicity (Panel B). The proportion of cells containing oligonucleotide remained high over the 120 hour period. The combination of 30 nM oligonucleotide and 2$\mu$g/ml GSV provided optimal uptake and minimal toxicity.

## EXAMPLE 17

The twenty-one oligonucleotides of Example 15 were then screened for their ability to inhibit IGF-I receptor mRNA levels in HaCaT cells, in accordance with the teachings herein. HaCaT cells were grown to 90% confluence in DMEM supplemented with 10% (v/v) FCS. Antisense oligonucleotides (30nM) were completed with cytofectin GSV (2$\mu$g/ml) and added tot he cells in the presence of serum. HaCaT keratinocytes were treated with the oligonucleotide/GSV complexes or randomized sequence oligonucleotides (R451, R766),

liposome alone (GSV), or were left untreated (UT). Duplicate treatments were performed. Repeat additions of the oligonucleotides/GSV complex were performed at 24, 48 and 76 hours following the first addition. Total RNA was isolated as per the RNAzolB protocol (Biotecx Laboratories, Inc. 6023 South Loop East, Houston, TX 77033) 96 hours following the first addition.

IGF-I receptor mRNA and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA levels were simultaneously determined by a ribonuclease (RNase) protection assay. The RNase Protection Assay kit, *in vitro* transcription kit, and IGF-I receptor and GAPDH DNA templates were obtained from Ambion, Inc. (2130 Woodward St., Houston, TX 78744). The amount of IGF-I receptor mRNA in any given sample was expressed as the amount of IGF-I receptor mRNA relative to the amount of GAPDH mRNA. Each oligonucleotide was tested in at least two separate experiments.

Figure 12 depicts representative results of the screening process. Panel A shows an electrophoretic analysis of IGF-I receptor and GAPDH mRNA fragments after RNase protection. Molecular weight markers are shown on the right hand side. The full-length probe is shown on the left hand side; G-probe indicates the IGF-I receptor probe. GAPDH protected fragments (G) are seen at 316 bases and IGF-I protected fragments (I) are seen at 276 bases. Exhibit E, Panel B provides a graph indicating the relative level of IGF-I receptor mRNA following each treatment.

The results obtaining from the above screening assays are summarized in Figure 13. The graph depicts the relative level of IGF-I receptor mRNA after treatment with oligonucleotides complementary to the human IGF-I receptor mRNA (26-86), four randomized sequence oligonucleotides (R1, R4, R7, R9), liposome alone (GSV), or no treatment (UT). Asterisks indicate a significant different in relative IGF-I receptor mRNA as compared to GSV treated cells ($n=4\text{-}10$, $p<0.05$).

As demonstrated in Figure 13, treatment with eighteen of the twenty-one oligonucleotides resulted in a significant different in levels of IGF-I receptor mRNA relative to GSV treated cells. Three of the antisense oligonucleotides tested in the screening assay reduce IGF-I receptor mRNA to less than 35% of GSV-treated cells. These antisense oligonucleotides have the following sequences, presented in the 5′ to 3′ direction:

#27 UCCGGAGCCAGACUU
#64 CACAGUUGCUGCAAG
#78 UCUCCGCUUCCUUUC

As further demonstrated in Figure 13, six of the antisense oligonucleotides tested in the screening assay reduce IGF-I receptor mRNA to between 35 and 50% of GSV-treated cells. These antisense oligonucleotides have the following sequences, presented in the 5′ to 3′ direction:

#28 AGCCCCCACAGCGAG
#32 GCCUUGGAGAUGAGC
#40 UAACAGAGGUCAGCA
#42 GGAUCAGGGACCAGU
#46 CGGCAAGCUACACAG
#50 GGCAGGCAGGCACAC

## EXAMPLE 19

Another experiment was performed demonstrating that antisense oligonucleotides targeted to genetic sequences encoding the IGF0I receptor and that reduce IGF-I receptor mRNA levels also inhibit the IGF-I receptor level on the surface of the treated cultured keratinocytes. HaCaT cells were grown to confluence in 24-well plates in DMEM containing 10% (v/v) FCS. Oligodeoxynucleotide and cytofectin GSV were mixed together in serum-free DMEM, and incubated at room temperature for 10 minutes before being diluted ten-fold in medium and placed on the cells. Cells were incubated for 72 hours with 30nM random sequence or

antisense oligonucleotide and 2$\mu$m/ml GSV, or with GSV alone in DMEM containing 10% (v/v) FCS with solutions replaced every 24 hours. This was followed by incubation with oligonucleotide/GSV in serum-free DMEM for 48 hours. All incubations were performed at 37°C. Cells were washed twice with 1ml cold PBS. Serum-free DMEM containing $10^{-10}$M $^{125}$I-IGF-I was added with or without the IGF-I analogue, des (1-3) IGF-I, at $10^{-11}$M to $10^{-7}$M. Cells were incubated at 4°C for 17 hours with gentle shaking, then washed three times with 1ml cold PBS and lysed in 250$\mu$l 0.5M NaOH/0.1% (v/v) Triton X-100 at room temperature for 4 hours. Specific binding of the solubilised cell extract was measured using a gamma counter. As shown in Figure 14, treatment of HaCaT keratinocytes with oligonucleotide reduced cell surface IGF-I receptor levels to 30% of levels in untreated keratinocytes or in keratinocytes treated with liposome alone or a random oligonucleotide, R766. As shown in Figure 15, treatment with oligonucleotide #27 also significantly reduced cell surface IGF-I receptor levels relative to untreated keratinocytes or treatment with liposome alone or random nucleotide R451. As demonstrated in Example 17, oligonucleotides #64 and #27 reduce IGF-I receptor mRNA levels in cultured keratinocytes to less than 35% of GSV-treated cells. Accordingly, the ability of an oligonucleotide to reduce IGF-I receptor mRNA levels in correlated with its ability to reduce cell surface IGF-I receptor levels.

The forgoing Examples demonstrate that antisense oligonucleotides targeted to the IGF-I receptor can be delivered to human keratinocytes *in vitro*, can inhibit IGF-I receptor mRNA levels in human keratinocytes *in vitro*, and that inhibition of mRNA levels is correlated with reduction of cell surface IGF-I receptor levels.

## EXAMPLE 19

Further experiments demonstrated the efficacy of antisense oligonucleotides targeted tot he IGF-I receptor in an *in vivo* model of psoriasis. An animal model of psoriasis is the human psoriatic skin xenograft model. The skin used in this model contains the true disease state. In this model, reduction in epidermal thickness of psoriatic grafts in response to treatment is positively correlated with efficacy of treatment. Both normal and psoriatic human skin were

grated into a thymic (nude) mice in accordance with a thymic (nude) mice in accordance with the methods of Baker *et al* (1992) *Brit. J. Dermatol.* 126:105 and Nanney *et al* (1992) *J. Invest. Dermatol,* 92:296. Successful grafting was achieved, as demonstrated in Figure 16, which shows hemotoxylin and eosin (H&E) stained sections of a 49-day old psoriatic human skin graft (Panel B) compared to the histology of the skin graft prior to grafting (Panel A). The histological features of psoriasis present in the pregraft section (e.g., parakeratosis, acanthosis and pronounced rete ridges) are present in the grafts more than seven weeks post grafting.

Using the model, oligonucleotide uptake was measured in epidermal keratinocytes *in vivo* after intradermal injection. Fluorescently labelled oligonucleotide (R451, 50$\mu$l, 10$\mu$M injection) was intradermally injected into psoriatic and normal skin grafts on a thymic mice. Live confocal microscopy and fluorescence microscopy of fixed sections was then employed. Using both techniques, oligonucleotide was found to localize in the nucleus of over 90% of basal keratinocytes. Figure 17 shows the nuclear localization of oligonucleotide in psoriatic skin cells using conventional fluorescence microscopy of a graft that was removed and sectioned after 24 hours.

After establishing oligonucleotide uptake in the *in vivo* model, a small number of pilots experiments were performed to determine a schedule for treatment of grated mice with antisense oligonucleotides targeted to genetic sequences encoding the IGF-I receptor. The treatment schedule was finalized as follows:

| Graft Number | Treatment | Volume of Injection | ODN Concentration | Duration of Treatment |
|---|---|---|---|---|
| 1-3 | Vehicle (PBS) | 50μl | - | 20 days |
| 4-6 | RandomODN#R451 | 50μl | 10μM | 20 days |
| 7-9 | ODN#27 | 50μl | 10μM | 20 days |
| 10-12 | ODN#74 | 50μl | 10μM | 20 days |
| 13-15 | ODN#50 | 50μl | 10μM | 20 days |

As determined above, oligonucleotide #27 (ODN #27) reduced IGF-I receptor mRNA *in vitro* to less than 35% of GSV-treated cells. Oligonucleotide #50 (ODN#50) reduced IGF-I receptor mRNA *in vitro* to between 35 and 50% of GSV-treated cells. Oligonucleotide #74 (ODN #74) was not inhibitory to IGF-I receptor mRNA *in vitro*. In the *in vivo* model, each mouse received two grafts. Random oligonucleotide or vehicle was injected intradermally in one graft and acted as a control. The second graft was injected with the targeted oligonucleotide. Each graft received an injection every second day for the duration of the treatment.

Histology of representative grafts from each treatment type are shown in Figures 18(a)-(d) and 19(a) - (d). Each sheet shows three images of H&E stained sections: the pregraft histology, the control treated graft, and the targeted oligonucleotide treated graft. Figures 18(a)-(d) are shown at 100x magnification; figures 19(a)-(d) are shown at 400x magnification. The total cross sectional area of epidermis of each graft was assessed using MCID analysis software. The pooled results from all of the treated grafts are shown in Figure 20.

As shown in Figures 18(a)-(d) and 19(a)-(d), the vehicle-treated (control) grafts were marginally thinner than thepregraft sections. The degree of regression in these experiments (ie., less than 10%) is not significant. A similar amount of marginal thinning

of epidermis compared to pregraft also occurred in pilot experiments in which psoriatic grafts were not injected, and thsu it is unlikely that the vehicle itself has any effect. Histological features of psoriasis present in skin samples prior to grafting (clubbing of rete ridges, parakeratosis, acanthosis) were present in these grafts.

The random oliognucleotide treated grafts varied in epidermal thickness after 20 days of treatment. Grafts were either a similar thickness to the pregraft histology, or marginally thinner. Random oligonucleotide treated grafts were in each case significantly thicker than their targeted oligonucleotide treated pairs.

As shown in Figure 20, the targeted oligonucleotide treated grafts were significantly thinner than the pregraft sections and showed less parakeratosis and clubbing of rete ridges. Antisense oligonucleotides which were effective at reducing IGF-I receptor mRNA levels *in vitro* (#27 and #50) produced greatere epidermal thinning than an oligonucleotide which was not inhibitory to IGF-I receptor mRNA *in vitro* (#74). Accordingly, there is a direct correlation between the ability of an oligonucleotide targeted to the IGF-I receptor to inhibit IGF-I receptor mRNA levels *in vitro* and the efficacy of the oligonucleotide as an anti-psoriasis agent in an *in vivo* model.

## EXAMPLE 20

Another experiment demonstrated that treatment of psoriatic grafts with an oligonucleotide targeted to a genetic sequence encoding the IGF-I receptor results in inhibition of proliferation. Pregrafts from psoriatic patients, control grafts treated with R4541, and grafts treated with oligonucleotide #27 were obtained as described in Example 19. An antibody to the cell cycle-specific nuclear antigen Ki67 was used to immunohistochemically detect actively dividing cells and tereby assess proliferation. The αKi67 antibody (DAKO, Glostrup, Denmark) recognizes the Ki67 antigen transiently expressed in nuclei of proliferating cells during late $G_1$, S, M and $G_2$ phases of the cycle and thsu provides a marker for proliferation. Pregraft and graft sections were immunohistochemically processed by standard methods using αKi67 (according to the

manufacturer's instructions), peroxidase-conjugated anti-rabbit second stage antibody, and a chromogenic peroxidase substrate.

The results of this experiment are presented in Figure 21 as immunohistochemical sections at 100x magnification. The top panel of Figure 21 depicts a pregraft section obtained from a psoriatic patient. The epidermis is thicker than normal and nucleic are evident in the stratum corneum. Ki67 positive cells, appearing as brown dots, are evidence in the basal and suprabasal layers, and indicate actively proliferating cells. The control (R450-treated) graft in the bottom panel of Figure 21 also exhibits evidence of proliferation, including parakeratosis and Ki67-positive cells appearing as brown-staining nuclei. The center panel of Figure 21 exhibits the oligonucleotide #27-treated graft. This graft exhibits significantly reduced proliferation as evidenced by normal (thin) epidermis, lack of invaginations, and substantial loss of Ki67-positive cells.

These results indicate that treatment of human psoriatic grafts with an oligonucleotide targeted to mRNA encoding the IGF-I receptor results in inhibition of epidermal proliferation.

## EXAMPLE 21

Topical formulations of complexes of oligonucleotides with cytofectin GSV in aqueous or methylcellulose gel formulations were prepared and assessed foruptake of the oligonucleotide by keratinocytes *in vivo*. The topical formulations contained oligonucleotides complexed with cytofectin GSV in an aqueous solution or methylcellulose carrier, as taught herein. With both aqueous and methylcellulose gel formulations, locatlization of oligonucleotide R451 to nuclei and cytoplasm of keratinocytes in normal human skin grafts on nuce mice was observed. Figure 22 shows an image from confocal microscopy demonstrating oligonucleotide locatlization in the nuclei and cytoplasm of keratinocytes in normal human skin grafts after topical application of fluroescently labeled oligonucleotide (10$\mu$M R451) complexed with cytofectin GSV (10$\mu$g/ml). Figure 23 shows an image from confocal microscopy demonstrating that topical application of the

same oligonucleotide/GSV concentrations in a 3% (w/v) methylcellulose gel produced similar uptake in the target keratinocyte population. Using an aqueous formulation of oligonucleotide/GSV complexes, penetration of oligonucleotide into the viable epidermis was observed, whereas application of formulations of oliognucleotide complexed with other cationic lipids resulted in localization of oligonucleotide in the stratum corneum.

**EXAMPLE 22**

Thirteen antisense oligonucleotides targeted to IGFBP-3 were synthesized. The antisense oligonucleotides are C5-propynyl-dU, Dc15 mer phosphorothioate oligodeoxyribonucleotides. Figure 24 attached hereto is a schematic diagram indicating the position of the thirteen oligonucleotides relative to the IGFBP-3 mRNA structure.

These oligonucleotides were screened for their ability to inhibit IGFBP-3 mRNA levels of HaCaT cells in accordance with the teachings herein. HaCaT cells were grown to 90% confluence in DMEM supplemented with 10% (v/v) FCS, then placed in complete keratinocyte serum free medium (KSFM, Gibco), which has a defined amount of EGF, for 24 hours. Oligonucleotides (30nM or 100nM) were complexed with GSV cytofectin (2$\mu$g/ml) and added to cells in complete KSFM to allow oligonucleotides to enter the nucleus before removal of EGF. Repeat additions were performed at three hours (in serum free DMEM, which releases the EGF inhibition of IGFBP-3 mRNA) and again after another 24 hours. HaCaT cells were also treated with randomized sequence oligonucleotides (R121, R451, R766 and R961), liposome alone (GSV) or were left untreated (UT). Total RNA was isolated as described in Example 17, 24 hours after the last treatment. Total RNA (15$\mu$g) was analyzed by Northern analysis and phosphoroimager quantitation for IGFBP-3 and GADPH mRNA. IGFBP-3 mRNA is expressed as the amount of IGFBP-3 mRNA relative to the amount of GAPDH mRNA.

Figures 25(a)-(d) provide graphs which depict results in this screening process. In these graphs, R1 and R12 refer to R121; R4, R4(0) and R45 rfer to R451; R7, R7(0) and R76 refer to R766; and R9 and R96 refer to R961. The values were standardized to GSV-

treated cells, and data was pooled and statistically analyzed by ANOVA followed by Domet's test to compare each treatment to GSV-treated cells. The pooled data are presented as a bar graph in Figure 26. As demonstrated, at a concentration of 30nM, treatment of HaCaT cells with 8 of the 12 targeted oligonucleotides tested resulted in a statistically significant reduction in levels of IGFBP-3 mRNA relative to GSV-treated cells. At a concentration of 100nM, treatment with 9 fo the 13 targeted oligonucleotides tested resulted in a statistically significant reduction in levels of IGFBP-3 mRNA relative to GSV-treated cells.

These experiments demonstrate that antisense oligonucleotides targeted to genetic sequences encoding IGFBP-3 can inhibit IGFBP-3 mRNA levels in human keratinocytes *in vitro*.

**EXAMPLE 23**

IGF-I receptor is a potent mitotic signalling molecule for keratinocytes and the human receptor elicits separate intracellular signals that prevent apoptosis (19). It is proposed in accordance with the present invention that inactivation of IGF-I receptors in epidermal keratinocytes will achieve three important outcomes in subsequent UV treatment of lesions:

(i) Acute epidermal hyperplasia following UV has been suggested to increase the risk of keratinocyte carcinogenic transformation (22). By reducing IGF-I receptor expression in the epidermis, the incidence of epidermal hyperplasia following UV exposure is likely to be reduced leading to an overall acceleration in normalization of the lesion and reduced carcinogenic risk.

(ii) Inhibition of anti-apoptotic action of IGF-I receptor will enhance the reversal of epidermal thickening and accelerate normalization of differentiation. Topical or injected IGF-I receptor antisense as adjunctive treatment will increase apoptosis in

the epidermal layer thereby enhancing the reduction in acanthosis observed in UV treatments.

(iii) Survival of keratinocytes, ie. those which evade apoptosis is likely to occur when cells have damaged DNA. Such mutations may be in the tumor suppressor region. Consequently, the use of antisense therapy will result in less frequent selection of mutated keratinocytes and therefore reduced incidence of basal cell carcinomas and squamous.

Accordingly, antisense therapy, especially against IGF-I-receptor is useful in combination with UV therapy in the treatment of epidermal hyperplasia.

## EXAMPLE 24

HaCaT cells were treated with antisense oligonucleotides directed to IGF-I receptor mRNA. Levels of IGF-I receptor mRNA were then monitored. In essence, confluent HaCaT cells were treated every 24 hours for four days with 2 $\mu$g/ml GSV lipid alone (GSV) or complexed with 30 nM IGF-I receptor specific oligonucleotides (#26 to #86) or random sequence oligonucleotides (*R121, R451 and R766*). Figure 27(a) is a photographic representation showing representative RNase protection assay gel showing IGF-I receptor (IGFR) and GAPDH mRNA in untreated or treated HaCaT cells. Figure 27(b) is a densitometric quantification of IGF-I receptor mRNA in a HaCaT cells following treatment with IGF-I receptor specific oligonucleotides (solid black) random sequence oligonucleotides (horizontal striped bar) or GSV alone (shaded bar) compared to untreated cells (UT, vertical striped bar).

## EXAMPLE 25

In this example, reduction in total cellular IGF-I receptor protein was monitored following antisense oligonucleotide treatment. Confluence HaCaT cells were treated with 24 hours for 4 days with 2 $\mu$g/ml GSV lipid alone (GSV) or complexed with 30 nM IGF-I receptor specific AONS (#27, #50 and #64) or the random sequence oligonucleotide, R451. Total

cellular protein was isolated and analysed for IGF-I receptor by SDS PAGE followed by western blotting with antibody specific for the human IGF-I receptor. Figure 28(a) shows duplicate treated cellular extracts following the IGF-I receptor at the predicted size of 110 kD. Figure 28(b) is a densitometric quantification of IGF-I receptor protein.

## EXAMPLE 26

The reduction in IGF-I receptor numbers was determined on the keratinocyte cell surface after antisense oligonucleotide treatment. HaCaT cells were tranfected with IGF-I receptor specific AONs #27, #50, #64, a random sequence oligonucleotides (R451) or following treatment with GSV a lipid alone every 24 hours for 4 days. Competition binding assays using $^{125}$I-IGF-I and the receptor-specific analogue, des(1-3)IGF-I were performed. Results are shown in Figure 29.

## EXAMPLE 27

In this example, the apoptotic protecting effects of IGF-I receptor on keratinocyte cells was tested by following the reduction in keratino cell numbers following antisense oligonucleotide treatment. HaCaT cells, initially at 40% confluence, were transfected with the IGF-I receptor specific AON #64, control sequences R451 and 6414 or treated with GSV a lipid alone every 24 hours for 2 days. The cell number was measured in culture wells using a dye binding assay. The results are presented in Figure 30. The results clearly confirm that the IGF-I receptor exhibits an anti-apoptotic effect. By reducing IGF-I receptor levels using antisense oligonucleotide treatment, the anti-apoptotic effect is interrupted and apoptosis results in the reduction in keratinocyte cell number. Results are shown in Figure 30.

## EXAMPLE 28

This example shows a reversal of epidermal hyperplasia in psoriatic human skin grafts on nude mice following intradermal injection with antisense oligonucleotides. Grafted psoriasis lesions were injected with IGF-I receptor specific AONs, a random sequence oligonucleotide in PBS, or with PBS alone, every 2 days for 20 days, then analysed

histologically. The results are shown in Figure 31. In Figure 31(a), donor A graft treated with AON #50 showing epidermal thinning compared with the pregraft and control (PBS) treated graft and donor graft treated with AON #27 showing epidermal thinning compared with pregraft and control (R451) treated graft. In Figure 31(b), the mean epidermal cross-sectional area over the full width of grafts is shown as determined by digital image analysis. The results show that epidermal hyperplasia is reversed following the intradermal injection of antisense oligonucleotides.

**EXAMPLE 29**

Figure 32 shows the reversal of epidermal hyperplasia correlating with reduced IGF-I receptor mRNA in grafted psoriasis lesions treated with antisense oligonucleotides. Figure 32(a) shows a psoriasis lesion prior to grafting and after grafting and treatment with IGF-I receptor specific oligonucleotide #27 (AON #27) or random sequence (R451) immunostained with antibodies to Ki67 to identify proliferating cells. Proliferating cells are indicated by a dark brown nucleus (arrows). Figure 32(b) shows the same lesion prior to grafting and after oligonucleotide treatment as in Figure 32(a) but subjected to *in situ* hybridisation with $^{35}$S-labelled cRNA probe complementary to the human IGF-I receptor mRNA. The presence of IGF-I receptor mRNA is indicated by silver grains which are almost eliminated in the epidermis of the lesion treated with IGF-I receptor specific oligonucleotide # 27 (AON #27). This experiment shows that reversal of epidermal hyperplasia correlates with reduced IGF-I receptor mRNA in grafted psoriasis lesions treated with antisense oligonucleotides.

**EXAMPLE 30**

Figure 33 treatment with oligonucleotides. HaCaT cell monolayers were grown to 90% confluence in DMEM containing 10% fetal calf serum treated every 24 hours for two days with 2 $\mu$g/ml GSV lipid alone (GSV) or complexed with 30 nM oligonucleotide. Total RNA was isolated and analysed for IGF-I receptor and GAPDH mRNA using a commercially available ribonuclease protection assay kit. The results show a reduction in IGF-I receptor mRNA in the HaCaT keratinocyte cells.

## EXAMPLE 31

Figure 34 treatment with oligonucleotides. HaCaT cell monolayers were grown to 90% confluence in DMEM containing 10% fetal calf serum treated every 24 hours for 4 days with 2 $\mu$g/ml GSV lipid alone (GSV) or complexed with 30 nM oligonucleotide. Cells were lysed in a buffer containing 50 mM HEPES, 150 mM NaCl, 10% v/v glycerol, 1 v/v Trison X-100 and 100 $\mu$g/ml aprotinin on ice for 30 minutes, then 30 $\mu$g of lysate was loaded onto a denaturing 7% w/v polyacrylamide gel followed by transfer onto an Immobilon-P membrane. Membranes were then incubated with anti-IGF-I receptor antibodies C20 (available from Santa Cruz Biotechnology Inc., Santa Cruz, California) for 1 hour at room temperature and developed using the Vistra ECF western blotting kit (Amersham). The results shown in Figure 34 confirm that IGF-I receptor protein is reduced in HaCaT keratinocytes following treatment with oligonucleotides.

## EXAMPLE 32

This example shows a reduction in HaCaT keratinocyte cell number following treatment with oligonucleotides. The results are shown in Figure 35. HaCaT cell monolayers were grown at 40% confluence in DMEM containing 10% fetal calf serum treated every 24 hours for 3 days with 2 $\mu$g/ml GSV lipid alone (GSV) or complexed with 15 nM oligonucleotide. Cell numbers were then measured every 24 hours using the amido black dye binding assay [32]. Results show that HaCaT keratino cells decrease in number following treatment with oligonucleotides due to a reduction in the anti-apoptotic effect of the IGF-I receptor.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

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CLAIMS:

1. A method for ameliorating the effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a mammal, said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation or a cell otherwise involved with said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing growth factor mediated cell proliferation and/or inflammation and/or other medical disorders.

2. A method according to claim 1 wherein cell proliferation and/or inflammation or other medical disorder is mediated by at least one of insulin-like growth factor I (IGF-I), keratinocyte growth factor (KGF), transforming growth factor-α (TGFα), tumour necrosis factor-α (TNFα), interleukin (IL) -1 (IL-1), IL-4, IL-6, IL-8 and/or basic fibroblast growth factor (bFGF).

3. A method according to claim 2 wherein cell proliferation and/or inflammation or other medical disorder is mediated by IGF-I.

4. A method according to claim 1 wherein the nucleic acid molecule inhibits or otherwise reduces IGF-I mediated cell proliferation and/or inflammation or other medical disorder.

5. A method according to claim 1 wherein the proliferative or inflammatory skin disorder is psoriasis, ichthyosis, pityriasis, rubra, pilaris, serborrhoea, keloids, keratosis, neoplasias, scleroderma, warts, benign growths or cancers of the skin.

6. A method according to claim 5 wherein the skin condition is psoriasis.

7. A method according to claim 1 wherein the other medical disorder is a hyperneovascular condition such as a neovascular condition of the retina, brain or skin, growth factor-mediated malignancies, other sclerotic disease, kidney disease or hyperproliferation of the inside of blood vessels or any other hyperplasia.

8. A method according to claim 1 or 4 or 6 or 7 wherein the mammal is a human.

9. A method according to claim 1 or 4 or 6 or 7 wherein the nucleic acid molecule is capable of inhibiting, reducing or otherwise interfering with IGF-I-interaction with its receptor.

10. A method according to claim 9 wherein the nucleic acid molecule is an antisense molecule capable of reducing expression of a gene encoding IGF-I, IGF-I-receptor or an IGF binding protein (IGFBP).

11. A method according to claim 10 wherein the nucleic acid molecule is an antisense molecule capable of reducing expression of a gene encoding IGFBP-2, -3, -4, -5 or -6.

12. A method according to claim 11 wherein the nucleic acid molecule is an antisense molecule capable of reducing expression of a gene encoding IGFBP-2 or IGFBP-3.

13. A method according to claim 10 or 12 wherein the antisense molecule is at least about 15 nucleotides in length and is capable of interacting with at least one sequence selected from the list set forth in Example 6 or Example 7 or Example 8.

14. A method according to claim 12 wherein the antisense molecule comprises the nucleotide sequence:

5'-ATCTCTCCGCTTCCTTTC-3' (<400>10)

15. A method according to claim 12 wherein the antisense molecule is selected from the following:

UCCGGAGCCAGACUU (<400>12)
CACAGUUGCUGCAAG (<400>13)
UCUCCGCUUCCUUUC (<400>14)
AGCCCCCACAGCGAG (<400>15)
GCCUUGGAGAUGAGC (<400>16)
UAACAGAGGUCAGCA (<400>17)
GGAUCAGGGACCAGU (<400>18)
CGGCAAGCUACACAG (<400>19)
GGCAGGCAGGCACAC (<400>20)

16. A method according to claim 15 wherein the antisense molecule in <400>12, <400>13 or <400>14.

17. A method according to claim 15 wherein the antisense molecule in <400>12.

18. A nucleic acid molecule comprising at least about 10 nucleotides capable of hybridising to or forming a heteroduplex or otherwise interacting with a complementary form of <400>12 to <400>20 inclusive.

19. A nucleic acid molecule comprising at least about 15 nucleotides capable of hybridising to or form a heteroduplex or otherwise interacting with a complementary form of <400>12 to <400>14 inclusive.

20. A method of ameliorating the effects of psoriasis or other medical disorder, said method comprising contacting proliferating skin or skin capable of proliferation or cell otherwise associated with said medical disorder with an effective amount of one or more nucleic acid molecules or chemical analogues thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation other medical disorder

wherein said one or more molecules comprises a polynucleotide capable of interacting with mRNA directed from an IGF-I gene, an IGF-I receptor gene or a gene encoding an IGFBP.

21. A method according to claim 20 wherein the IGFBP is IGFBP-2 or IGFBP-3.

22. A method according to claim 20 or 21 wherein the mammal is a human.

23. A method according to claim 22 wherein the nucleic acid molecule is capable of interacting with a nucleotide sequence selected from the list set forth in <400>12 to <400>14 inclusive.

24. A method according to claim 23 wherein the nucleic acid molecule comprises the nucleotide sequence selected from <400>12 to <400>14.

25. A composition comprising a nucleic acid molecule capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation or other medical disorder said composition further comprising one or more pharmaceutically acceptable carriers and/or diluents.

26. A composition according to claim 25 wherein the nucleic acid molecule is antisense molecule to a gene encoding IGF-I, IGF-I-receptor or an IGFBP.

27. A composition according to claim 26 wherein the nucleic acid molecule is selected from <400>12 to <400>20 inclusive.

28. A composition according to claim 26 selected from <400>12 to <400>14 inclusive.

29. A method for ameliorating the effects of a proliferative and/or inflammatory skin disorder such as psoriasis said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation with effective amounts of UV treatment and a nucleic acid molecule or chemical

analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or inflammation.

30. A method according to claim 29 wherein the proliferative or inflammatory skin disorder is psoriasis, ichthyosis, pityriasis, rubra, pilaris, serborrhoea, keloids, keratosis, neoplasias, scleroderma, warts, benign growths or cancers of the skin.

31. A method according to claim 30 wherein the proliferative or inflammatory skin disorder is psoriasis.

32. A method according to claim 29 or 30 or 31 wherein the nucleic acid molecule is capable of inhibiting, reducing or otherwise interfering with IGF-I-interaction with its receptor.

33. A method according to claim 32 wherein the nucleic acid molecule is an antisense molecule capable of reducing expression of a gene encoding IGF-I, IGF-I-receptor or an IGF binding protein (IGFBP).

34. A method according to claim 33 wherein the nucleic acid molecule is an antisense molecule capable of reducing expression of a gene encoding IGFBP-2, -3, -4, -5 or -6.

35. A method according to claim 34 wherein the nucleic acid molecule is an antisense molecule capable of reducing expression of a gene encoding IGFBP-2 or IGFBP-3.

36. A method according to claim 33 wherein the nucleic acid molecule is an antisense molecule capable of reducing expression of a gene encoding IGF-I receptor.

37. A method according to any one of claims 29 to 36 wherein the antisense molecule is at least about 15 nucleotides in length and is capable of interacting with at least one sequence selected from the list set forth in Example 6 or Example 7 or Example 8.

38. A method according to claim 37 wherein the antisense molecule comprises the nucleotide sequence:

5'-ATCTCTCCGCTTCCTTTC-3' (<400>10)

39. A method according to claim 37 wherein the antisense molecule is selected from the following:

UCCGGAGCCAGACUU (<400>12)
CACAGUUGCUGCAAG (<400>13)
UCUCCGCUUCCUUUC (<400>14)
AGCCCCCACAGCGAG (<400>15)
GCCUUGGAGAUGAGC (<400>16)
UAACAGAGGUCAGCA (<400>17)
GGAUCAGGGACCAGU (<400>18)
CGGCAAGCUACACAG (<400>19)
GGCAGGCAGGCACAC (<400>20)

40. A method according to claim 39 wherein the antisense molecule in <400>12, <400>13 or <400>14.

41. A method according to claim 40 wherein the antisense molecule in <400>12.

42. A method according to claim 39 wherein the UV treatment occurs simultaneously with or following contact with the nucleic acid molecule or its chemical analogue.

43. Use of an antisense molecule directed to the gene encoding IGF-I receptor or its mRNA as adjunct therapy in combination with UV treatment to reduce proliferation and/or inflammation of keratinocyte cells.

44. Use according to claim 43 in the treatment of psoriasis.

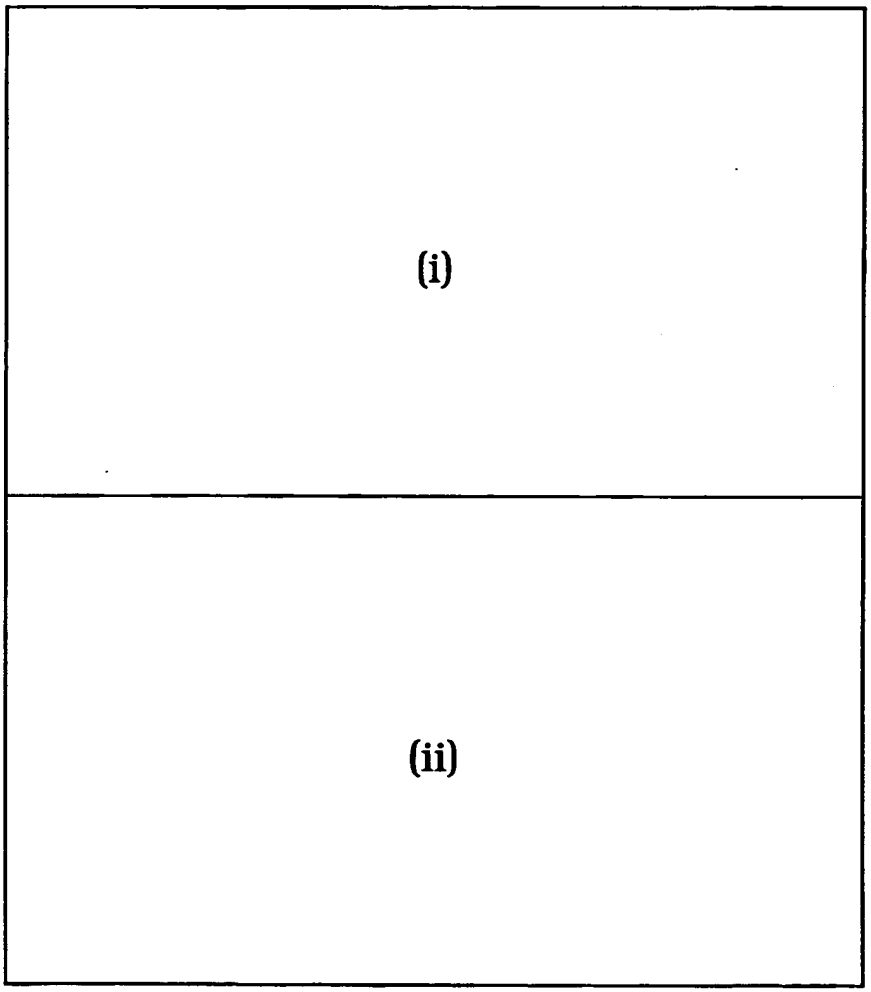


Figure 1

```
1     ATTCGGGGCG AGGGAGGAGG AAGAAGCGGA GGAGGCGGCT CCCGCTCGCA
51    GGGCCGTGCA CCTGCCCGCC CGCCCGCTCG CTCGCTCGCC CGCCGCGCCG
101   CGCTGCCGAC CGCCAGCATG CTGCCGAGAG TGGGCTGCCC CGCGCTGCCG
151   CTGCCGCCGC CGCCGCTGCT GCCGCTGCTG CCGCTGCTGC TGCTGCTACT
201   GGGCGCGAGT GGCGGCGGCG GCGGGGCGCG CGCGGAGGTG CTGTTCCGCT
251   GCCCGCCCTG CACACCCGAG CGCCTGGCCG CCTGCGGGCC CCCGCCGGTT
301   GCGCCGCCCG CCGCGGTGGC CGCAGTGGCC GGAGGCGCCC GCATGCCATG
351   CGCGGAGCTC GTCCGGGAGC CGGGCTGCGG CTGCTGCTCG GTGTGCGCCC
401   GGCTGGAGGG CGAGGCGTGC GGCGTCTACA CCCCGCGCTG CGGCCAGGGG
451   CTGCGCTGCT ATCCCCACCC GGGCTCCGAG CTGCCCCTGC AGGCGCTGGT
501   CATGGGCGAG GGCACTTGTG AGAAGCGCCG GGACGCCGAG TATGGCGCCA
551   GCCCGGAGCA GGTTGCAGAC AATGGCGATG ACCACTCAGA AGGAGGCCTG
601   GTGGAGAACC ACGTGGACAG CACCATGAAC ATGTTGGGCG GGGGAGGCAG
651   TGCTGGCCGG AAGCCCCTCA AGTCGGGTAT GAAGGAGCTG GCCGTGTTCC
701   GGGAGAAGGT CACTGAGCAG CACCGGCAGA TGGGCAAGGG TGGCAAGCAT
```

Figure 1(i)

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751   CACCTTGGCC TGGAGGAGCC CAAGAAGCTG CGACCACCCC CTGCCAGGAC
801   TCCCTGCCAA CAGGAACTGG ACCAGGTCCT GGAGCGGATC TCCACCATGC
851   GCCTTCCGGA TGAGCGGGGC CCTCTGGAGC ACCTCTACTC CCTGCACATC
901   CCCAACTGTG ACAAGCATGG CCTGTACAAC CTCAAACAGT GCAAGATGTC
951   TCTGAACGGG CAGCGTGGGG AGTGCTGGTG TGTGAACCCC AACACCGGGA
1001  AGCTGATCCA GGGAGCCCCC ACCATCCGGG GGGACCCCGA GTGTCATCTC
1051  TTCTACAATG AGCAGCAGGA GGCTTGCGGG GTGCACACCC AGCGGATGCA
1101  GTAGACCGCA GCCAGCCGGT GCCTGGCGCC CCTGCCCCCC GCCCCTCTCC
1151  AAACACCGGC AGAAAACGGA GAGTGCTTGG GTGGTGGGTG CTGGAGGATT
1201  TTCCAGTTCT GACACACGTA TTTATATTTG GAAAGAGACC AGCACCGAGC
1251  TCGGCACCTC CCCGGCCTCT CTCTTCCCAG CTGCAGATGC CACACCTGCT
1301  CCTTCTTGCT TTCCCCGGGG GAGGAAGGGG GTTGTGGTCG GGGAGCTGGG
1351  GTACAGGTTT GGGGAGGGGG AAGAGAAATT TTTATTTTTG AACCCCTGTG
1401  TCCCTTTTGC ATAAGATTAA AGGAAGGAAA AGT
```

Figure 1(ii)

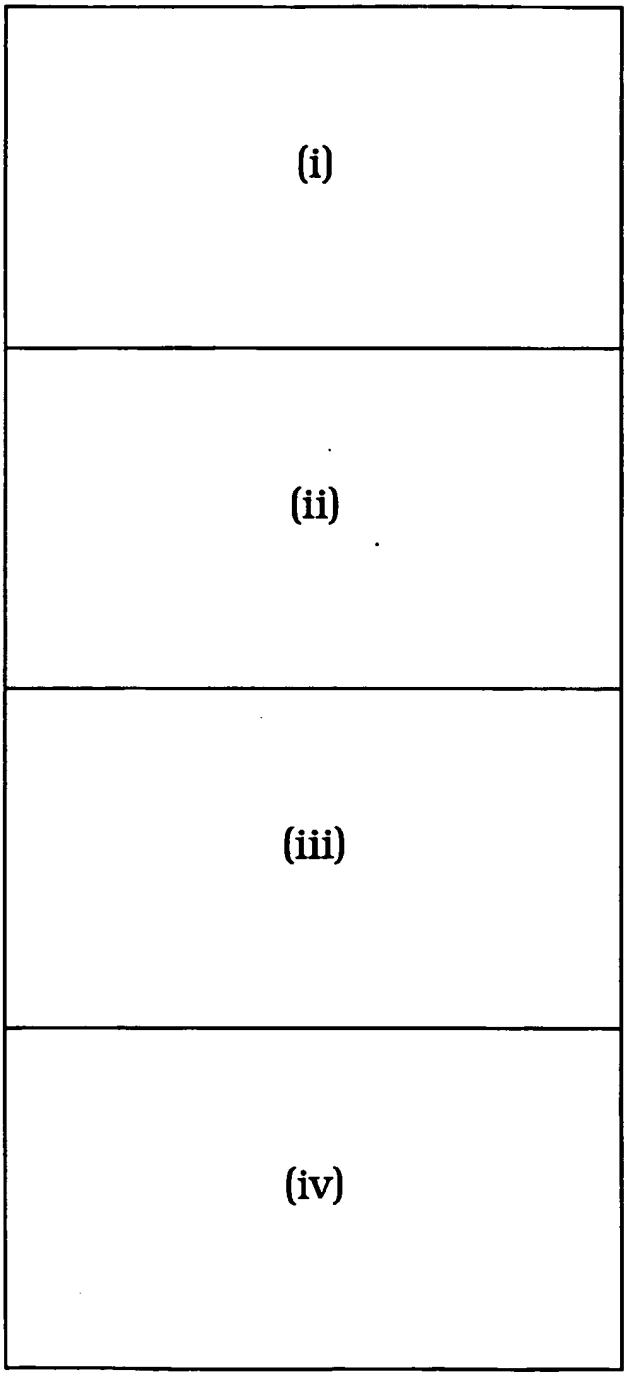


Figure 2

```
1    CTCAGCGCCC AGCCGCTTCC TGCCTGGATT CCACAGCTTC GCGCCGTGTA
51   CTGTCGCCCC ATCCCTGCGC GCCCAGCCTG CCAAGCAGCG TGCCCCGGTT
101  GCAGGCGTCA TGCAGCGGGC GCGACCCACG CTCTGGGCCG CTGCGCTGAC
151  TCTGCTGGTG CTGCTCCGCG GGCCGCCGGT GGCGCGGGCT GGCGCGAGCT
201  CGGGGGGCTT GGGTCCCGTG GTGCGCTGCG AGCCGTGCGA CGCGCGTGCA
251  CTGGCCCAGT GCGCGCCTCC GCCCGCCGTG TGCGCGGAGC TGGTGCGCGA
301  GCCGGGCTGC GGCTGCTGCC TGACGTGCGC ACTGAGCGAG GGCCAGCCGT
351  GCGGCATCTA CACCGAGCGC TGTGGCTCCG GCCTTCGCTG CCAGCCGTCG
401  CCCGACGAGG CGCGACCGCT GCAGGCGCTG CTGGACGGCC GCGGGCTCTG
451  CGTCAACGCT AGTGCCGTCA GCCGCCTGCG CGCCTACCTG CTGCCAGCGC
501  CGCCAGCTCC AGGAAATGCT AGTGAGTCGG AGGAAGACCG CAGCGCCGGC
551  AGTGTGGAGA GCCCGTCCGT CTCCAGCACG CACCGGGTGT CTGATCCCAA
601  GTTCCACCCC CTCCATTCAA AGATAATCAT CATCAAGAAA GGGCATGCTA
651  AAGACAGCCA GCGCTACAAA GTTGACTACG AGTCTCAGAG CACAGATACC
701  CAGAACTTCT CCTCCGAGTC CAAGCGGGAG ACAGAATATG GTCCCTGCCG
```

Figure 2(i)

```
751   TAGAGAAATG GAAGACACAC TGAATCACCT GAAGTTCCTC AATGTGCTGA
801   GTCCCAGGGG TGTACACATT CCCAACTGTG ACAAGAAGGG ATTTTATAAG
851   AAAAAGCAGT GTCGCCCTTC CAAAGGCAGG AAGCGGGGCT TCTGCTGGTG
901   TGTGGATAAG TATGGGCAGC CTCTCCCAGG CTACACCACC AAGGGGAAGG
951   AGGACGTGCA CTGCTACAGC ATGCAGAGCA AGTAGACGCC TGCCGCAAGT
1001  TAATGTGGAG CTCAAATATG CCTTATTTTG CACAAAAGAC TGCCAAGGAC
1051  ATGACCAGCA GCTGGCTACA GCCTCGATTT ATATTTCTGT TTGTGGTGAA
1101  CTGATTTTTT TTAAACCAAA GTTTAGAAAG AGGTTTTTGA AATGCCTATG
1151  GTTTCTTTGA ATGGTAAACT TGAGCATCTT TTCACTTTCC AGTAGTCAGC
1201  AAAGAGCAGT TTGAATTTTC TTGTCGCTTC CTATCAAAAT ATTCAGAGAC
1251  TCGAGCACAG CACCCAGACT TCATGCGCCC GTGGAATGCT CACCACATGT
1301  TGGTCGAAGC GGCCGACCAC TGACTTTGTG ACTTAGGCGG CTGTGTTGCC
1351  TATGTAGAGA ACACGCTTCA CCCCCACTCC CCGTACAGTG CGCACAGGCT
1401  TTATCGAGAA TAGGAAAACC TTTAAACCCC GGTCATCCGG ACATCCCAAC
1451  GCATGCTCCT GGAGCTCACA GCCTTCTGTG GTGTCATTTC TGAAACAAGG
```

Figure 2(ii)

```
1501  GCGTGGATCC CTCAACCAAG AAGAATGTTT ATGTCTTCAA GTGACCTGTA
1551  CTGCTTGGGG ACTATTGGAG AAAATAAGGT GGAGTCCTAC TTGTTTAAAA
1601  AATATGTATC TAAGAATGTT CTAGGGCACT CTGGGAACCT ATAAAGGCAG
1651  GTATTTCGGG CCCTCCTCTT CAGGAATCTT CCTGAAGACA TGGCCCAGTC
1701  GAAGGCCCAG GATGGCTTTT GCTGCGGCCC CGTGGGGTAG GAGGGACAGA
1751  GAGACGGGAG AGTCAGCCTC CACATTCAGA GGCATCACAA GTAATGGCAC
1801  AATTCTTCGG ATGACTGCAG AAAATAGTGT TTTGTAGTTC AACAACTCAA
1851  GACGAAGCTT ATTTCTGAGG ATAAGCTCTT TAAAGGCAAA GCTTTATTTT
1901  CATCTCTCAT CTTTTGTCCT CCTTAGCACA ATGTAAAAAA GAATAGTAAT
1951  ATCAGAACAG GAAGGAGGAA TGGCTTGCTG GGGAGCCCAT CCAGGACACT
2001  GGGAGCACAT AGAGATTCAC CCATGTTTGT TGAACTTAGA GTCATTCTCA
2051  TGCTTTTCTT TATAATTCAC ACATATATGC AGAGAAGATA TGTTCTTGTT
2101  AACATTGTAT ACAACATAGC CCCAAATATA GTAAGATCTA TACTAGATAA
2151  TCCTAGATGA AATGTTAGAG ATGCTATATG ATACAACTGT GGCCATGACT
2201  GAGGAAAGGA GCTCACGCCC AGAGACTGGG CTGCTCTCCC GGAGGCCAAA
```

Figure 2(iii)

```
2251  CCCAAGAAGG TCTGGCAAAG TCAGGCTCAG GGAGACTCTG CCCTGCTGCA
2301  GACCTCGGTG TGGACACACG CTGCATAGAG CTCTCCTTGA AAACAGAGGG
2351  GTCTCAAGAC ATTCTGCCTA CCTATTAGCT TTTCTTTATT TTTTTAACTT
2401  TTTGGGGGGA AAAGTATTTT TGAGAAGTTT GTCTTGCAAT GTATTTATAA
2451  ATAGTAAATA AAGTTTTTAC CATT
```

Figure 2(iv)

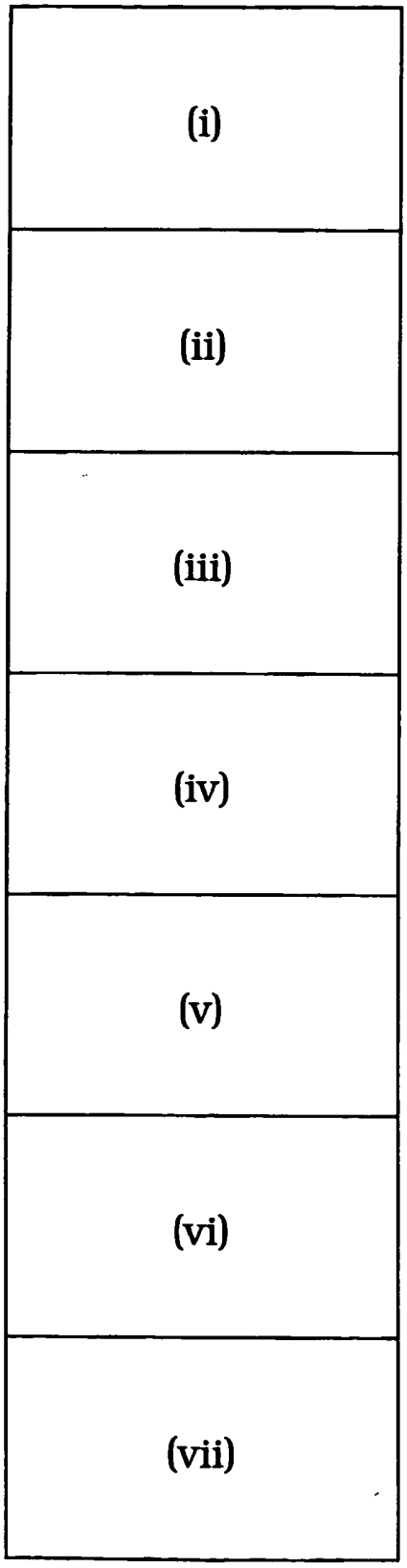


Figure 3

```
1    TTTTTTTTT TTTTGAGAAA GGGAATTTCA TCCCAAATAA AAGGAATGAA
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101  TCTCCGCCGC GCTCTCGCTC TGGCCGACGA GTGGAGAAAT CTGCGGGCCA
151  GGCATCGACA TCCGCAACGA CTATCAGCAG CTGAAGCGCC TGGAGAACTG
201  CACGGTGATC GAGGGCTACC TCCACATCCT GCTCATCTCC AAGGCCGAGG
251  ACTACCGCAG CTACCGCTTC CCCAAGCTCA CGGTCATTAC CGAGTACTTG
301  CTGCTGTTCC GAGTGGCTGG CCTCGAGAGC CTCGGAGACC TCTTCCCCAA
351  CCTCACGGTC ATCCGCGGCT GGAAACTCTT CTACAACTAC GCCCTGGTCA
401  TCTTCGAGAT GACCAATCTC AAGGATATTG GGCTTTACAA CCTGAGGAAC
451  ATTACTCGGG GGGCCATCAG GATTGAGAAA AATGCTGACC TCTGTTACCT
501  CTCCACTGTG GACTGGTCCC TGATCCTGGA TGCGGTGTCC AATAACTACA
551  TTGTGGGGAA TAAGCCCCCA AAGGAATGTG GGGACCTGTG TCCAGGGACC
601  ATGGAGGAGA AGCCGATGTG TGAGAAGACC ACCATCAACA ATGAGTACAA
651  CTACCGCTGC TGGACCACAA ACCGCTGCCA GAAAATGTGC CCAAGCACGT
701  GTGGGAAGCG GGCGTGCACC GAGAACAATG AGTGCTGCCA CCCCGAGTGC
```

Figure 3(i)

```
751   CTGGGCAGCT GCAGCGCGCC TGACAACGAC ACGGCCTGTG TAGCTTGCCG
801   CCACTACTAC TATGCCGGTG TCTGTGTGCC TGCCTGCCCG CCCAACACCT
851   ACAGGTTTGA GGGCTGGCGC TGTGTGGACC GTGACTTCTG CGCCAACATC
901   CTCAGCGCCG AGAGCAGCGA CTCCGAGGGG TTTGTGATCC ACGACGGCGA
951   GTGCATGCAG GAGTGCCCCT CGGGCTTCAT CCGCAACGGC AGCCAGAGCA
1001  TGTACTGCAT CCCTTGTGAA GGTCCTTGCC CGAAGGTCTG TGAGGAAGAA
1051  AAGAAAACAA AGACCATTGA TTCTGTTACT TCTGCTCAGA TGCTCCAAGG
1101  ATGCACCATC TTCAAGGGCA ATTTGCTCAT TAACATCCGA CGGGGGAATA
1151  ACATTGCTTC AGAGCTGGAG AACTTCATGG GGCTCATCGA GGTGGTGACG
1201  GGCTACGTGA AGATCCGCCA TTCTCATGCC TTGGTCTCCT TGTCCTTCCT
1251  AAAAAACCTT CGCCTCATCC TAGGAGAGGA GCAGCTAGAA GGGAATTACT
1301  CCTTCTACGT CCTCGACAAC CAGAACTTGC AGCAACTGTG GGACTGGGAC
1351  CACCGCAACC TGACCATCAA AGCAGGGAAA ATGTACTTTG CTTTCAATCC
1401  CAAATTATGT GTTTCCGAAA TTTACCGCAT GGAGGAAGTG ACGGGGACTA
1451  AAGGGCGCCA AAGCAAAGGG GACATAAACA CCAGGAACAA CGGGGAGAGA
```

Figure 3(ii)

```
1501  GCCTCCTGTG AAAGTGACGT CCTGCATTTC ACCTCCACCA CCACGTCGAA
1551  GAATCGGCATC ATCATAACCT GGCACCGGTA CCGGCCCCCT GACTACAGGG
1601  ATCTCATCAG CTTCACCGTT TACTACAAGG AAGCACCCTT TAAGAATGTC
1651  ACAGAGTATG ATGGGCAGGA TGCCTGCGGC TCCAACAGCT GGAACATGGT
1701  GGACGTGGAC CTCCCGCCCA ACAAGGACGT GGAGCCCGGC ATCTTACTAC
1751  ATGGGCTGAA GCCCTGGACT CAGTACGCCG TTTACGTCAA GGCTGTGACC
1801  CTCACCATGG TGGAGAACGA CCATATCCGT GGGGCCAAGA GTGAGATCTT
1851  GTACATTCGC ACCAATGCTT CAGTTCCTTC CATTCCCTTG GACGTTCTTT
1901  CAGCATCGAA CTCCTCTTCT CAGTTAATCG TGAAGTGGAA CCCTCCCTCT
1951  CTGCCCAACG GCAACCTGAG TTACTACATT GTGCGCTGGC AGCGGCAGCC
2001  TCAGGACGGC TACCTTTACC GGCACAATTA CTGCTCCAAA GACAAAATCC
2051  CCATCAGGAA GTATGCCGAC GGCACCATCG ACATTGAGGA GGTCACAGAG
2101  AACCCCAAGA CTGAGGTGTG TGGTGGGGAG AAAGGGCCTT GCTGCGCCTG
2151  CCCCAAAACT GAAGCCGAGA AGCAGGCCGA GAAGGAGGAG GCTGAATACC
2201  GCAAAGTCTT TGAGAATTTC CTGCACAACT CCATCTTCGT GCCCAGACCT
```

Figure 3(iii)

```
2251  GAAAGGAAGC GGAGAGATGT CATGCAAGTG GCCAACACCA CCATGTCCAG
2301  CCGAAGCAGG AACACCACGG CCGCAGACAC CTACAACATC ACCGACCCGG
2351  AAGAGCTGGA GACAGAGTAC CCTTTCTTTG AGAGCAGAGT GGATAACAAG
2401  GAGAGAACTG TCATTTCTAA CCTTCGGCCT TTCACATTGT ACCGCATCGA
2451  TATCCACAGC TGCAACCACG AGGCTGAGAA GCTGGGCTGC AGCGCCTCCA
2501  ACTTCGTCTT TGCAAGGACT ATGCCCGCAG AAGGAGCAGA TGACATTCCT
2551  GGGCCAGTGA CCTGGGAGCC AAGGCCTGAA AACTCCATCT TTTTAAAGTG
2601  GCCGGAACCT GAGAATCCCA ATGGATTGAT TCTAATGTAT GAAATAAAAT
2651  ACGGATCACA AGTTGAGGAT CAGCGAGAAT GTGTGTCCAG ACAGGAATAC
2701  AGGAAGTATG GAGGGGCCAA GCTAAACCGG CTAAACCCGG GGAACTACAC
2751  AGCCCGGATT CAGGCCACAT CTCTCTCTGG GAATGGGTCG TGGACAGATC
2801  CTGTGTTCTT CTATGTCCAG GCCAAAACAG GATATGAAAA CTTCATCCAT
2851  CTGATCATCG CTCTGCCCGT CGCTGTCCTG TTGATCGTGG GAGGGTTGGT
2901  GATTATGCTG TACGTCTTCC ATAGAAAGAG AAATAACAGC AGGCTGGGGA
2951  ATGGAGTGCT GTATGCCTCT GTGAACCCGG AGTACTTCAG CGCTGCTGAT
```

Figure 3(iv)

```
3001  GTGTACGTTC CTGATGAGTG GGAGGTGGCT CGGGAGAAGA TCACCATGAG
3051  CCGGGAACTT GGGCAGGGGT CGTTTGGGAT GGTCTATGAA GGAGTTGCCA
3101  AGGGTGTGGT GAAAGATGAA CCTGAAACCA GAGTGGCCAT TAAAACAGTG
3151  AACGAGGCCG CAAGCATGCG TGAGAGGATT GAGTTTCTCA ACGAAGCTTC
3201  TGTGATGAAG GAGTTCAATT GTCACCATGT GGTGCGATTG CTGGGTGTGG
3251  TGTCCCAAGG CCAGCCAACA CTGGTCATCA TGGAACTGAT GACACGGGGC
3301  GATCTCAAAA GTTATCTCCG GTCTCTGAGG CCAGAAATGG AGAATAATCC
3351  AGTCCTAGCA CCTCCAAGCC TGAGCAAGAT GATTCAGATG GCCGGAGAGA
3401  TTGCAGACGG CATGGCATAC CTCAACGCCA ATAAGTTCGT CCACAGAGAC
3451  CTTGCTGCCC GGAATTGCAT GGTAGCCGAA GATTTCACAG TCAAAATCGG
3501  AGATTTTGGT ATGACGCGAG ATATCTATGA GACAGACTAT TACCGGAAAG
3551  GAGGCAAAGG GCTGCTGCCC GTGCGCTGGA TGTCTCCTGA GTCCCTCAAG
3601  GATGGAGTCT TCACCACTTA CTCGGACGTC TGGTCCTTCG GGGTCGTCCT
3651  CTGGGAGATC GCCACACTGG CCGAGCAGCC CTACCAGGGC TTGTCCAACG
3701  AGCAAGTCCT TCGCTTCGTC ATGGAGGGCG GCCTTCTGGA CAAGCCAGAC
```

Figure 3(v)

```
3751  AACTGTCCTG ACATGCTGTT TGAACTGATG CGCATGTGCT GGCAGTATAA
3801  CCCCAAGATG AGGCCTTCCT TCCTGGAGAT CATCAGCAGC ATCAAAGAGG
3851  AGATGGAGCC TGGCTTCCGG GAGGTCTCCT TCTACTACAG CGAGGAGAAC
3901  AAGCTGCCCG AGCCGGAGGA GCTGGACCTG GAGCCAGAGA ACATGGAGAG
3951  CGTCCCCCTG GACCCCTCGG CCTCCTCGTC CTCCCTGCCA CTGCCCGACA
4001  GACACTCAGG ACACAAGGCC GAGAACGGCC CCGGCCCTGG GGTGCTGGTC
4051  CTCCGCGCCA GCTTCGACGA GAGACAGCCT TACGCCCACA TGAACGGGGG
4101  CCGCAAGAAC GAGCGGGCCT TGCCGCTGCC CCAGTCTTCG ACCTGCTGAT
4151  CCTTGGATCC TGAATCTGTG CAAACAGTAA CGTGTGCGCA CGCGCAGCGG
4201  GGTGGGGGGG GAGAGAGAGT TTTAACAATC CATTCACAAG CCTCCTGTAC
4251  CTCAGTGGAT CTTCAGTTCT GCCCTTGCTG CCCGCGGGAG ACAGCTTCTC
4301  TGCAGTAAAA CACATTTGGG ATGTTCCTTT TTTCAATATG CAAGCAGCTT
4351  TTTATTCCCT GCCCAAACCC TTAACTGACA TGGGCCTTTA AGAACCTTAA
4401  TGACAACACT TAATAGCAAC AGAGCACTTG AGAACCAGTC TCCTCACTCT
4451  GTCCCTGTCC TTCCCTGTTC TCCCTTTCTC TCTCCTCTCT GCTTCATAAC
```

Figure 3(vi)

```
4501  GGAAAAATAA TTGCCACAAG TCCAGCTGGG AAGCCCTTTT TATCAGTTTG
4551  AGGAAGTGGC TGTCCCTGTG GCCCCATCCA ACCACTGTAC ACACCCGCCT
4601  GACACCGTGG GTCATTACAA AAAAACACGT GGAGATGGAA ATTTTTACCT
4651  TTATCTTTCA CCTTTCTAGG GACATGAAAT TTACAAAGGG CCATCGTTCA
4701  TCCAAGGCTG TTACCATTTT AACGCTGCCT AATTTTGCCA AAATCCTGAA
4751  CTTTCTCCCT CATCGGCCCG GCGCTGATTC CTCGTGTCCG GAGGCATGGG
4801  TGAGCATGGC AGCTGGTTGC TCCATTTGAG AGACACGCTG GCGACACACT
4851  CCGTCCATCC GACTGCCCCT GCTGTGCTGC TCAAGGCCAC AGGCACACAG
4901  GTCTCATTGC TTCTGACTAG ATTATTATTT GGGGGAACTG GACACAATAG
4951  GTCTTTCTCT CAGTGAAGGT GGGGAGAAGC TGAACCGGC
```

Figure 3 (vii)

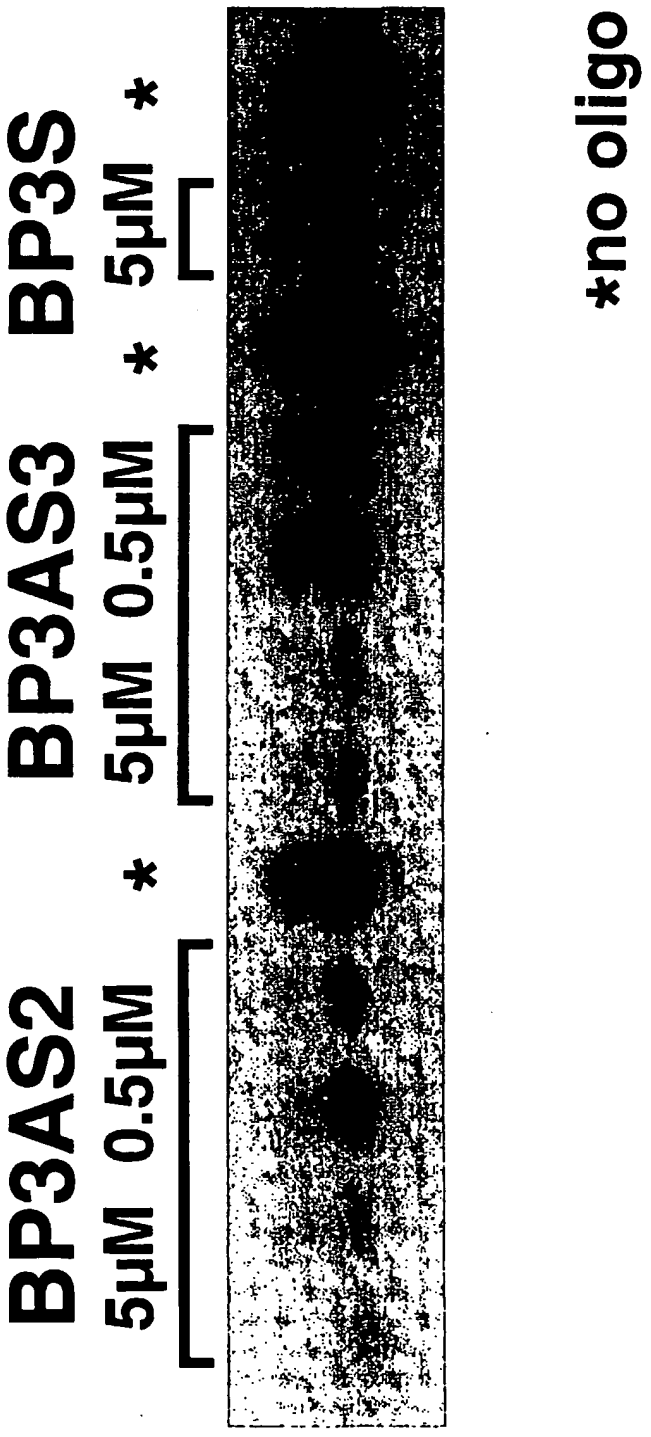



Figure 4a

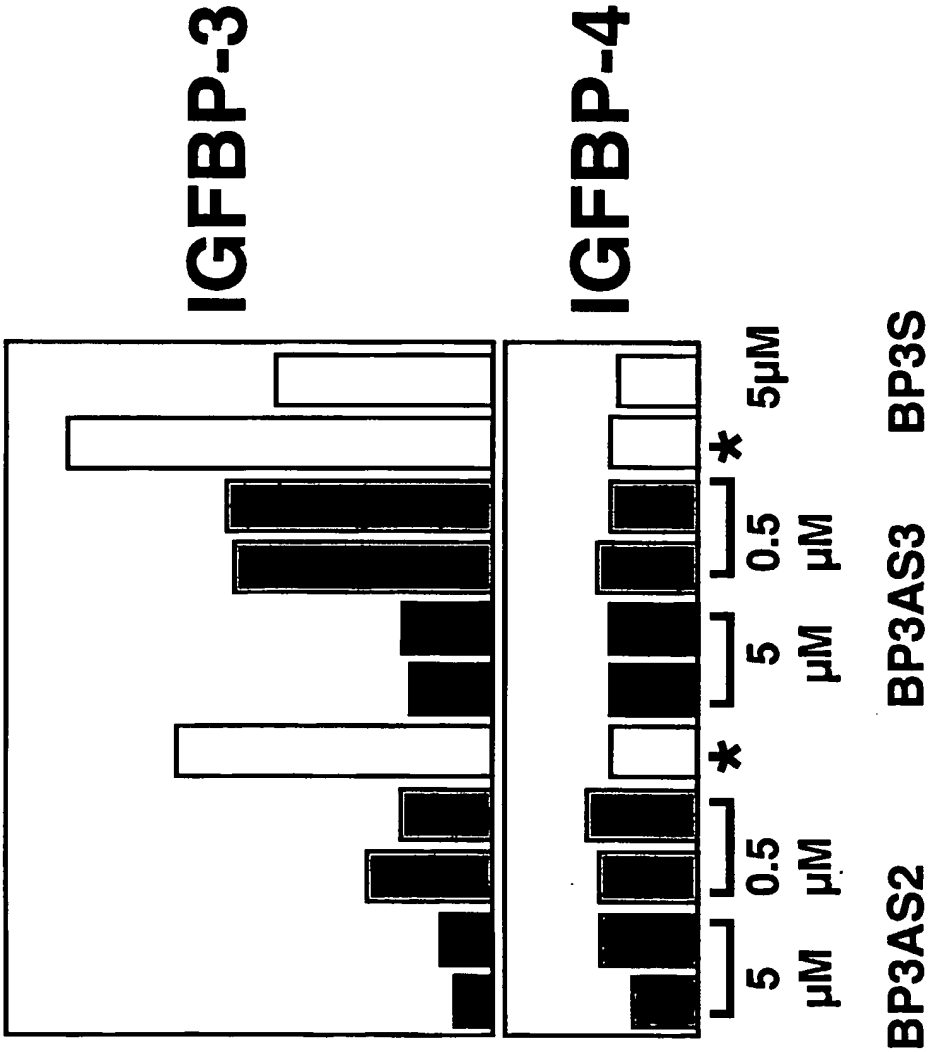



Figure 4b

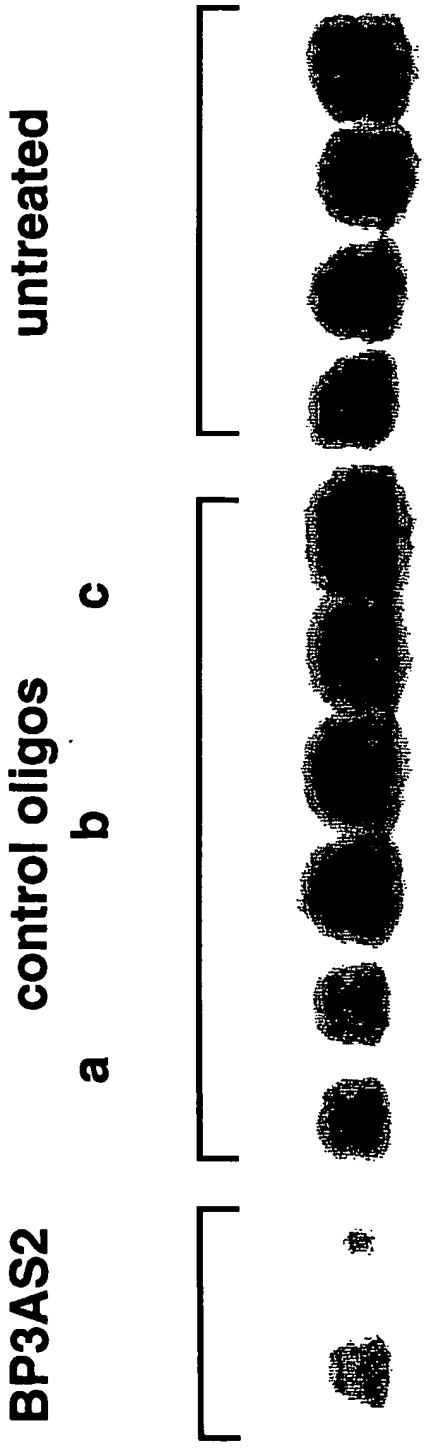



Figure 5a

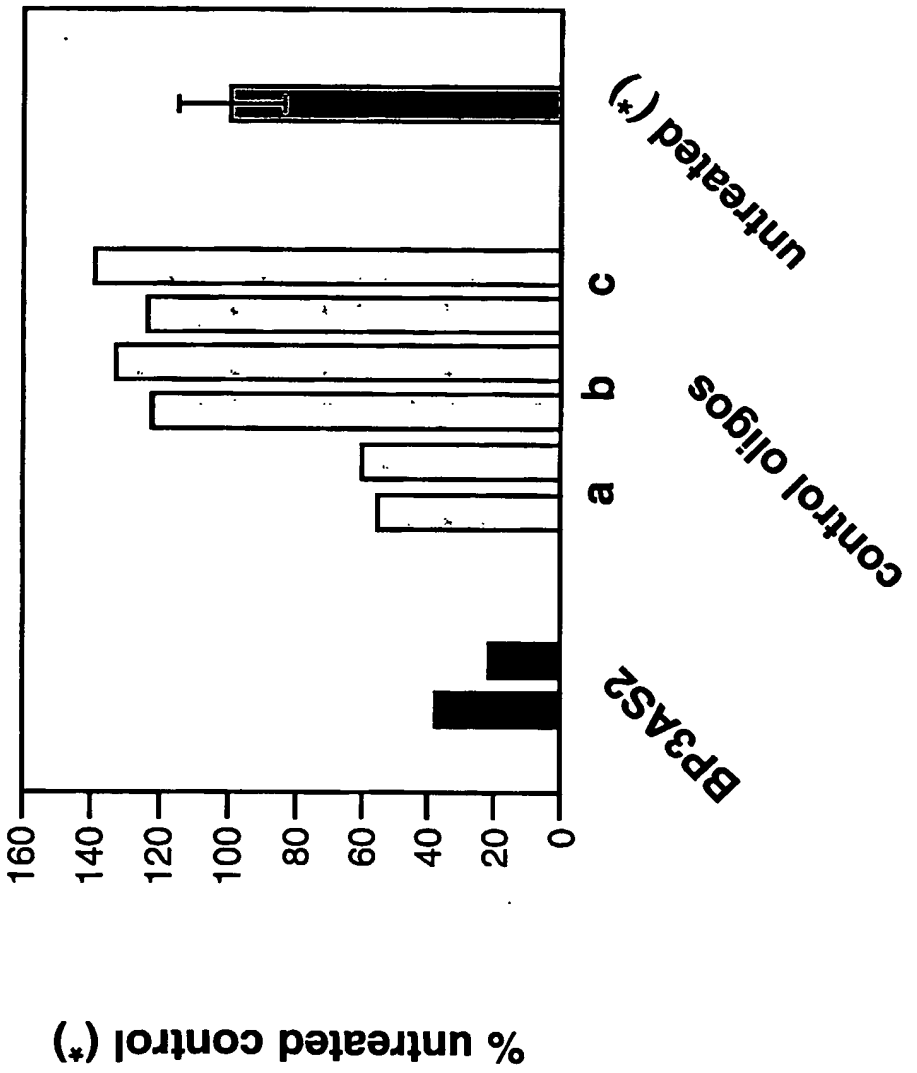

% untreated control (*)
160
140
120
100
80
60
40
20
0
BP3AS2
control oligos
a
b
c
untreated (*)

Figure 5b

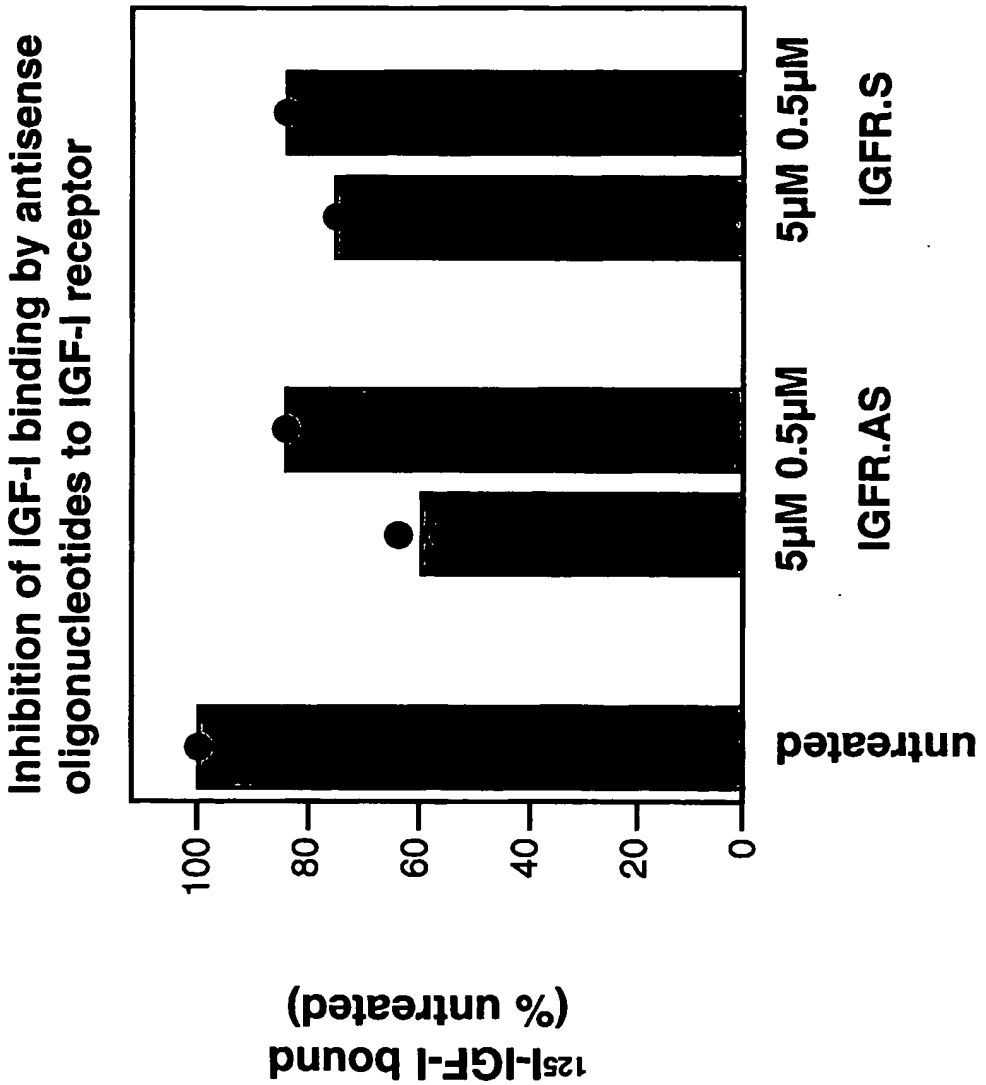

Inhibition of IGF-I binding by antisense oligonucleotides to IGF-I receptor
125I-IGF-I bound (% untreated)
100
80
60
40
20
0
untreated
5µM 0.5µM
IGFR.AS
5µM 0.5µM
IGFR.S

Figure 6

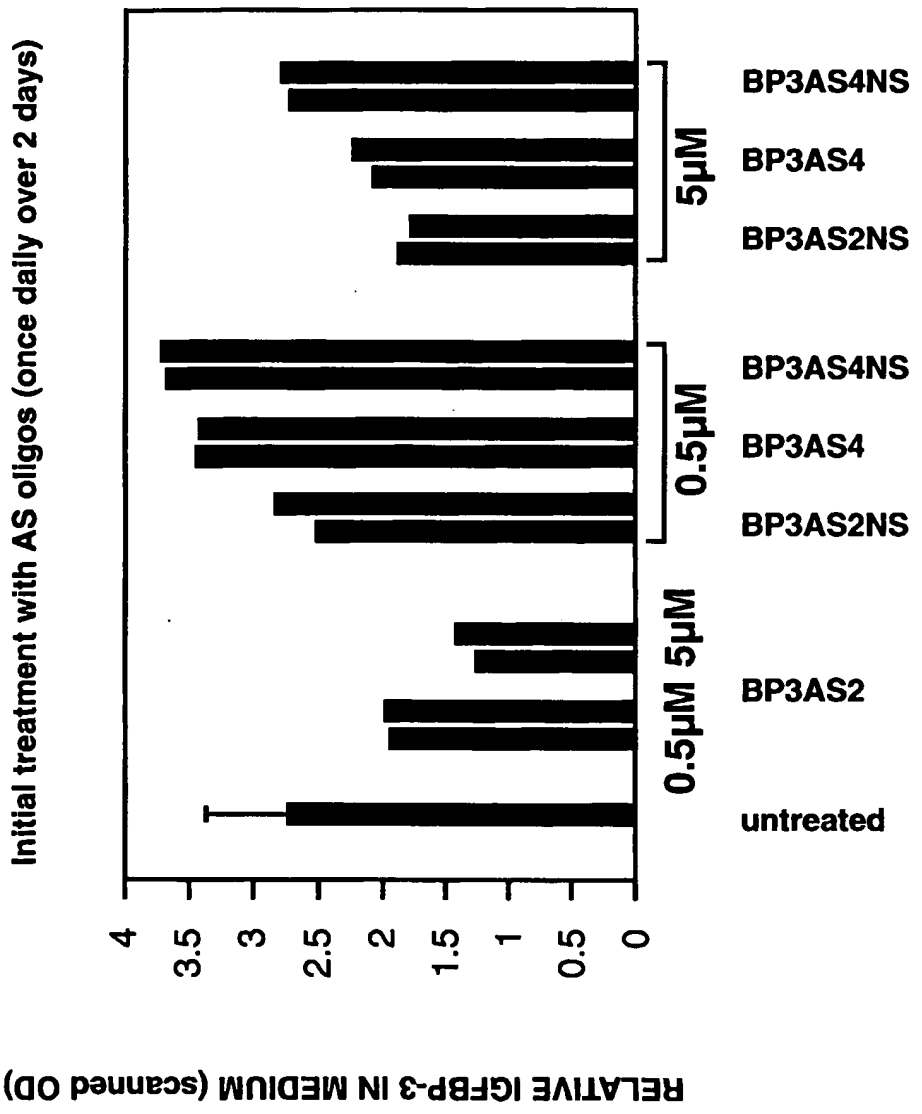

Initial treatment with AS oligos (once daily over 2 days)
BP3AS4NS
BP3AS4
BP3AS2NS
5μM
BP3AS4NS
BP3AS4
BP3AS2NS
0.5μM
BP3AS2
0.5μM 5μM
untreated
4
3.5
3
2.5
2
1.5
1
0.5
0
RELATIVE IGFBP-3 IN MEDIUM (scanned OD)

Figure 7

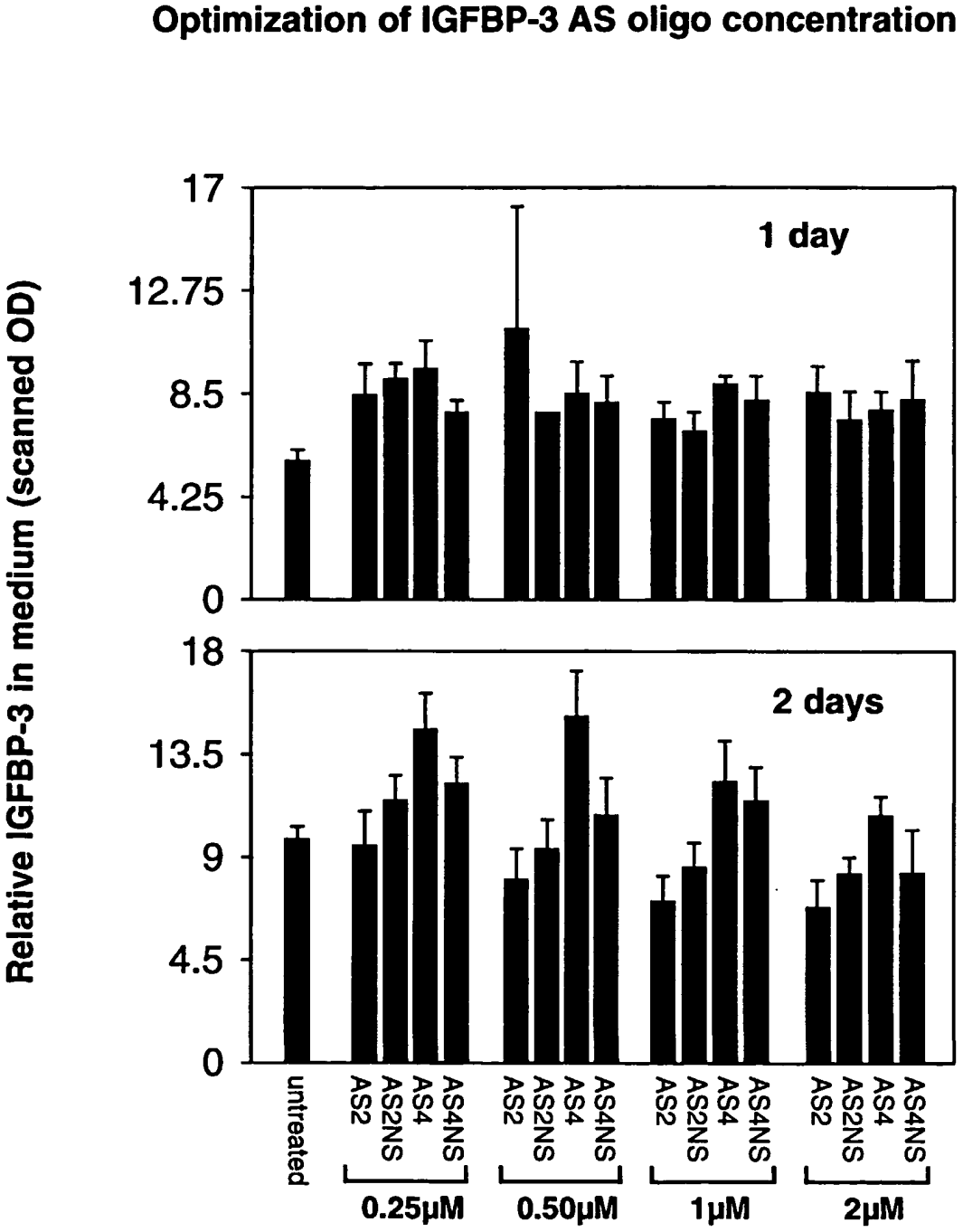

Optimization of IGFBP-3 AS oligo concentration
Relative IGFBP-3 in medium (scanned OD)
17
12.75
8.5
4.25
0
1 day
18
13.5
9
4.5
0
2 days
untreated
AS2
AS2NS
AS4
AS4NS
0.25μM
0.50μM
1μM
2μM

Figure 8

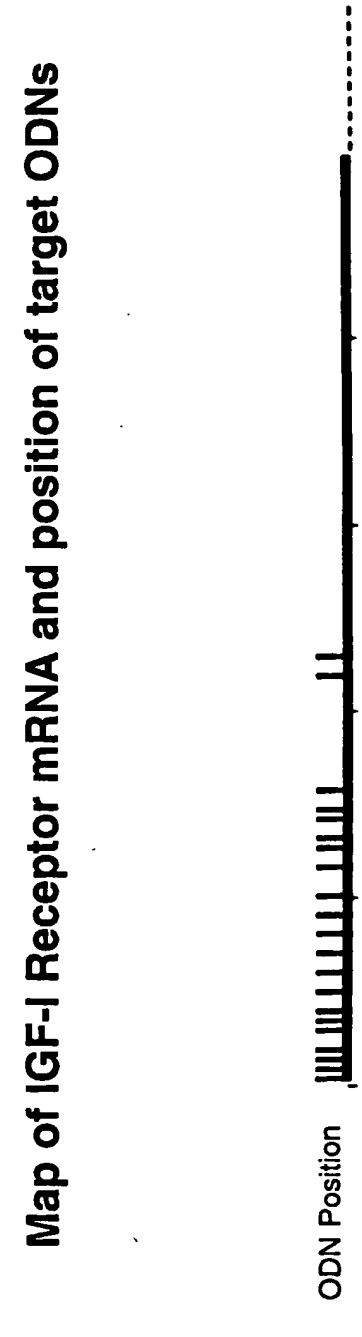
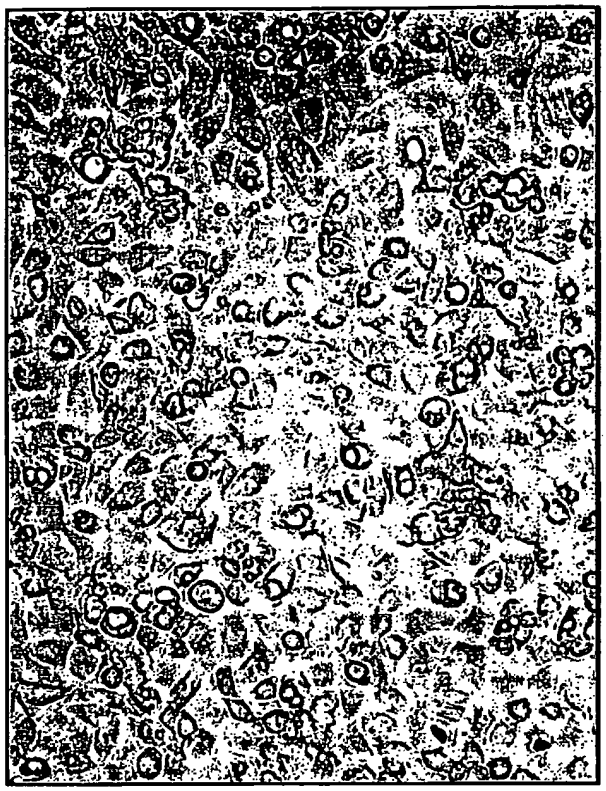
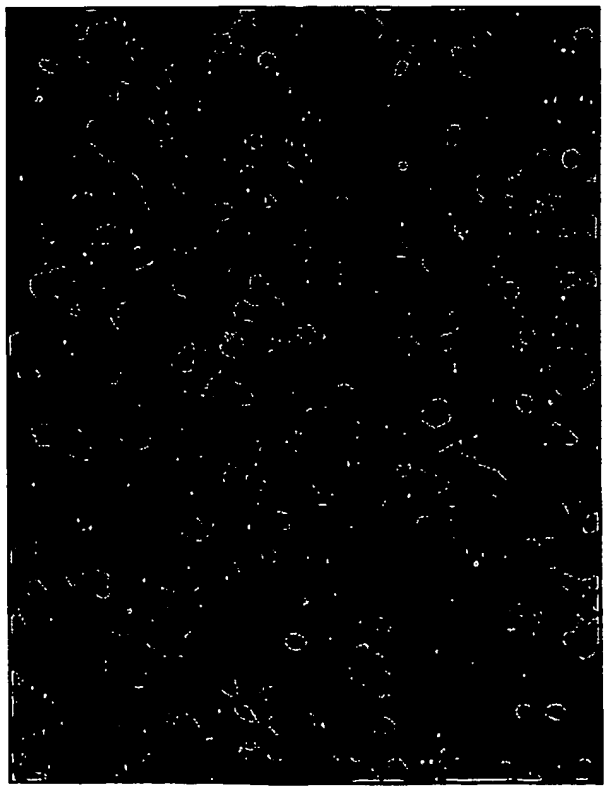

Map of IGF-I Receptor mRNA and position of target ODNs
ODN Position
0
1000
2000
3000
4000
IGF-I R protein
alpha -subunit
beta -subunit
•Position of the 21 tested ODNs ( I )
•mRNA transcript lengths = 7Kb and 11Kb
•coding sequence 46-4149

Figure 9

Lipid-mediated uptake of oligonucleotide in keratinocytes



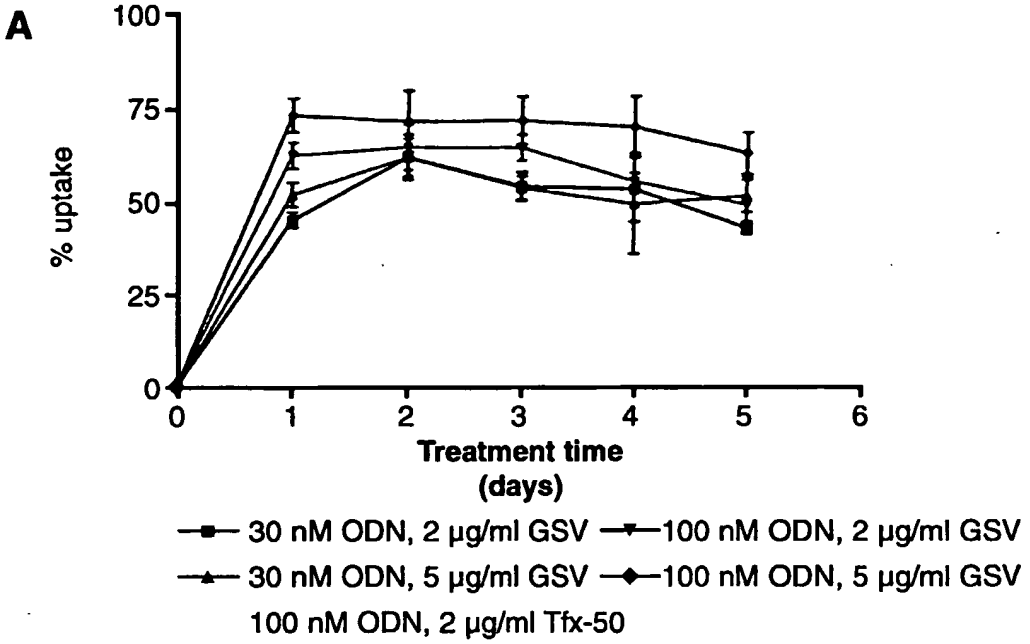
B



A

Figure 10

## Uptake (A) and toxicity (B) of ODN/ lipid complexes in keratinocytes



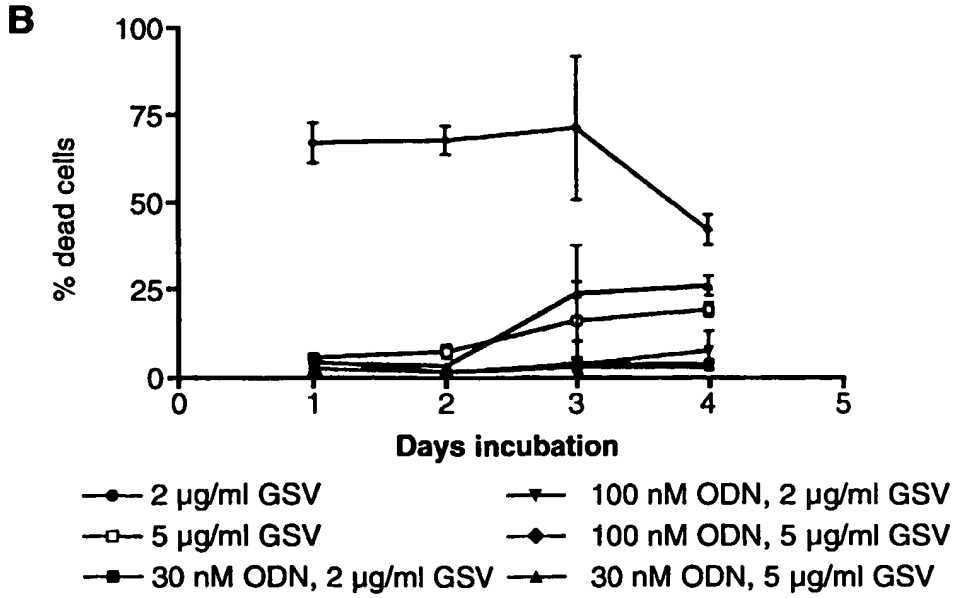
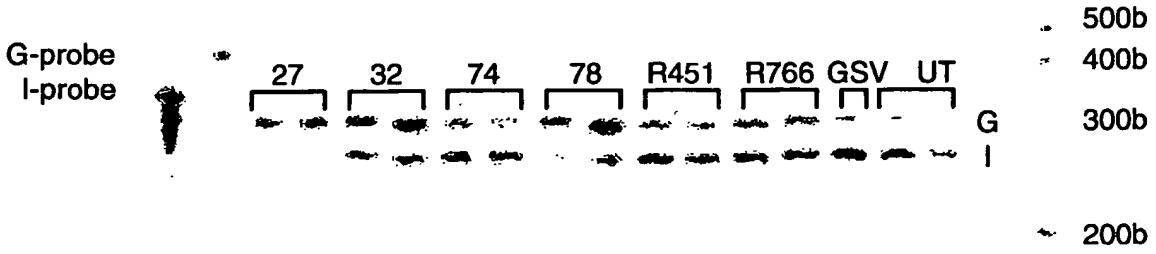




Figure 11

## IGF-I Receptor mRNA in ODN treated (30nM) HaCaT cells (2µg/ml GSV)

**A**




**B**

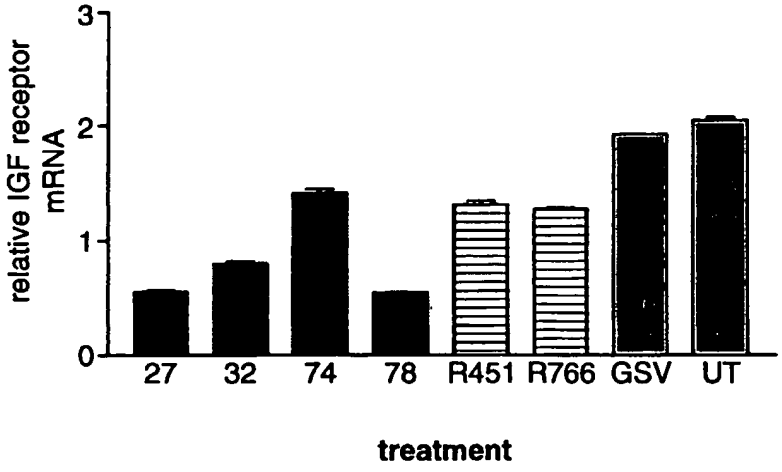



Figure 12

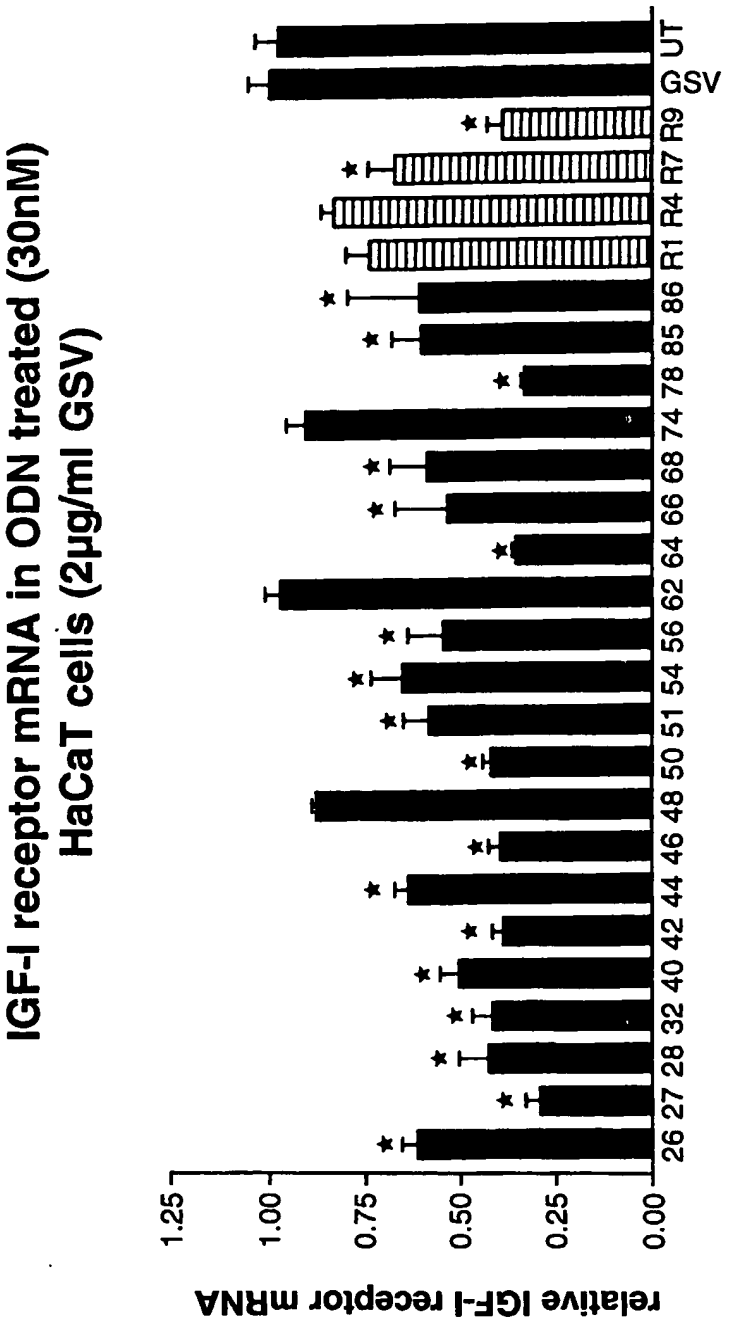

IGF-I receptor mRNA in ODN treated (30nM)
HaCaT cells (2µg/ml GSV)
relative IGF-I receptor mRNA
1.25
1.00
0.75
0.50
0.25
0.00
26 27 28 32 40 42 44 46 48 50 51 54 56 62 64 66 68 74 78 85 86 R1 R4 R7 R9 GSV UT
Treatment

Figure 13

**Effect of antisense oligonucleotides on IGF-1 receptor levels on the surface of keratinocytes:**
**Competition Assay - $^{125}$I IGF-1 vs Des 1-3 IGF-1**

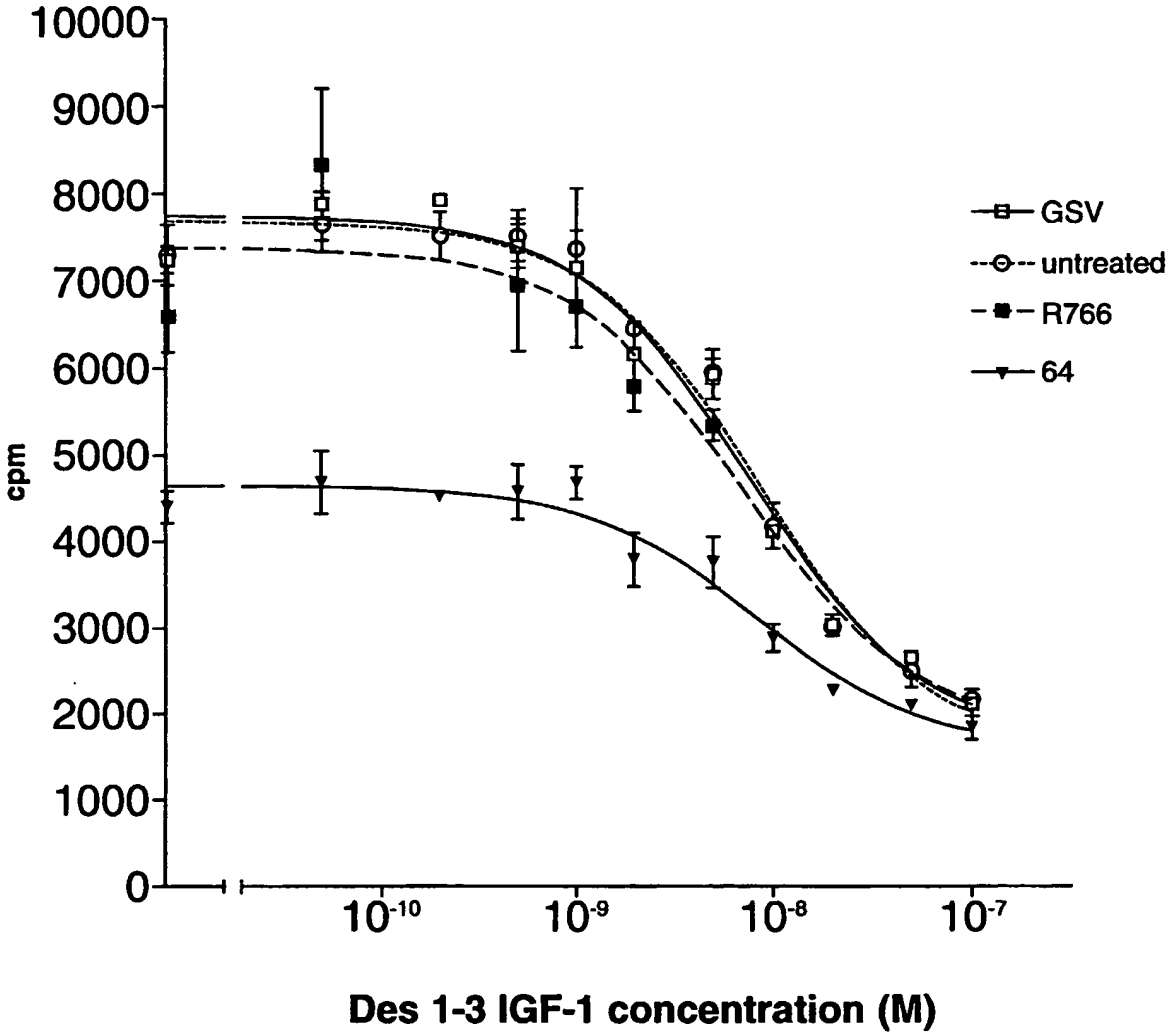



Figure 14

**Effect of antisense oligonucleotides on IGF-1 receptor levels on the surface of keratinocytes:**
**Competition Assay - $^{125}$I IGF-1 vs Des 1-3 IGF-1**

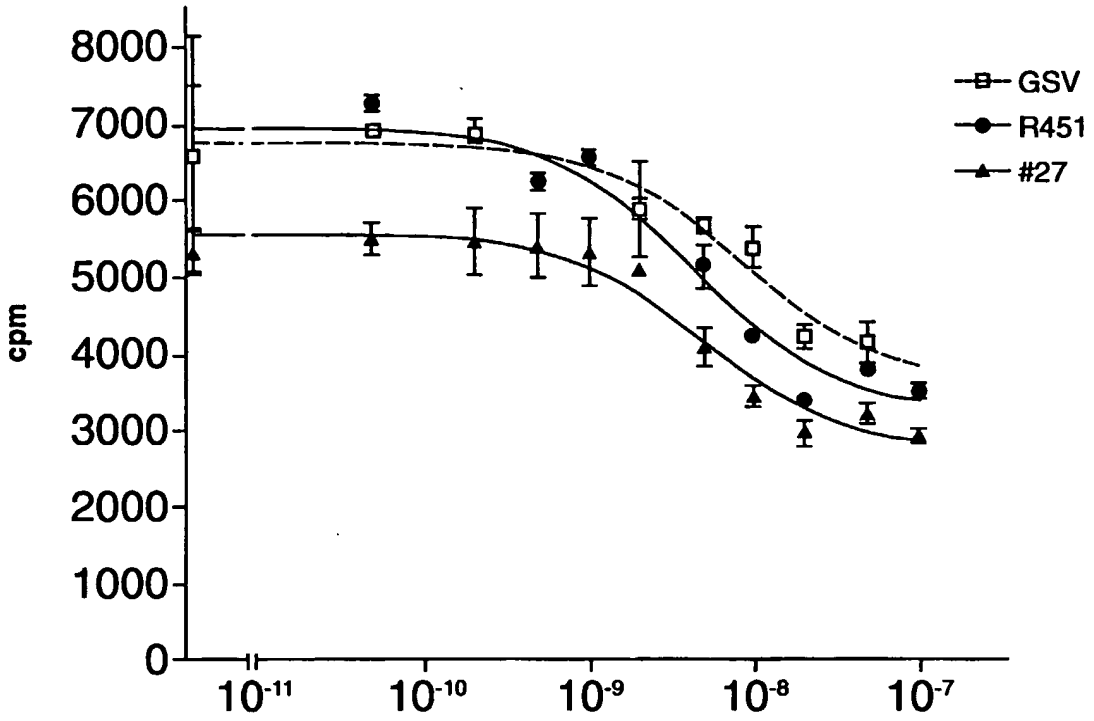



Figure 15

H&E stained sections of (A) psoriatic skin biopsy prior to grafting and (B) 49 day old psoriatic skin graft using skin from same donor

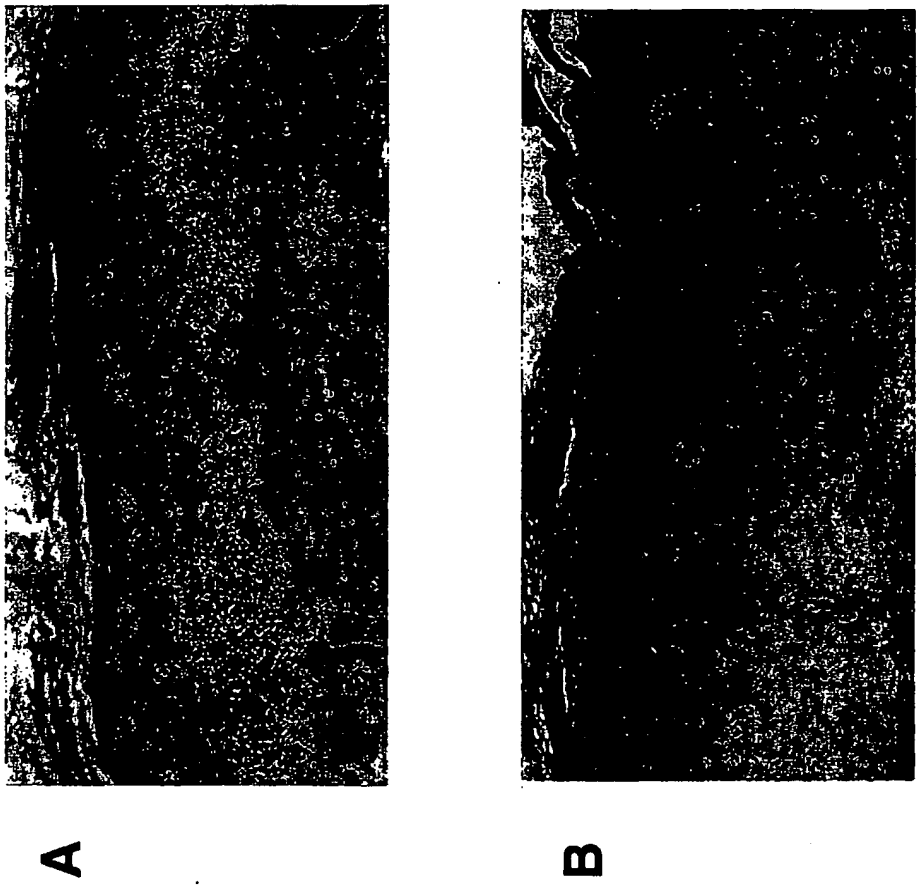



Figure 16

Uptake of oligonucleotide after intradermal injection into psoriatic skin graft on a nude mouse

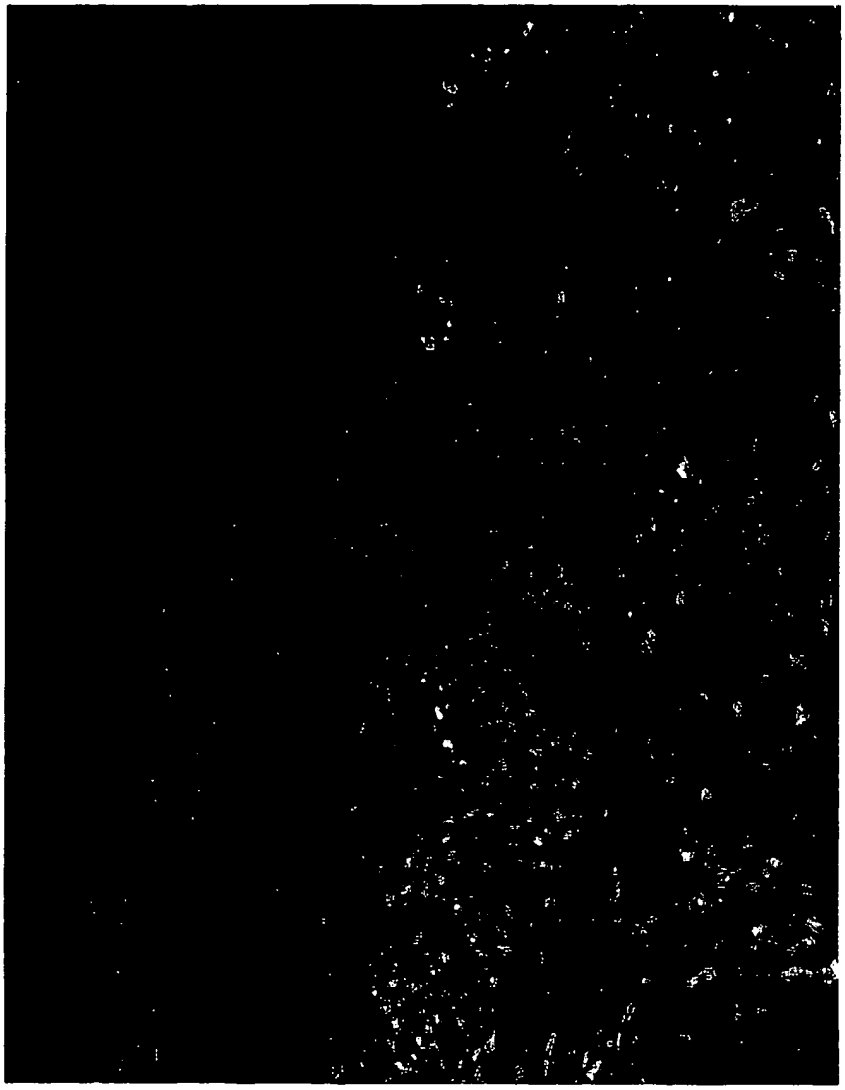


Figure 17

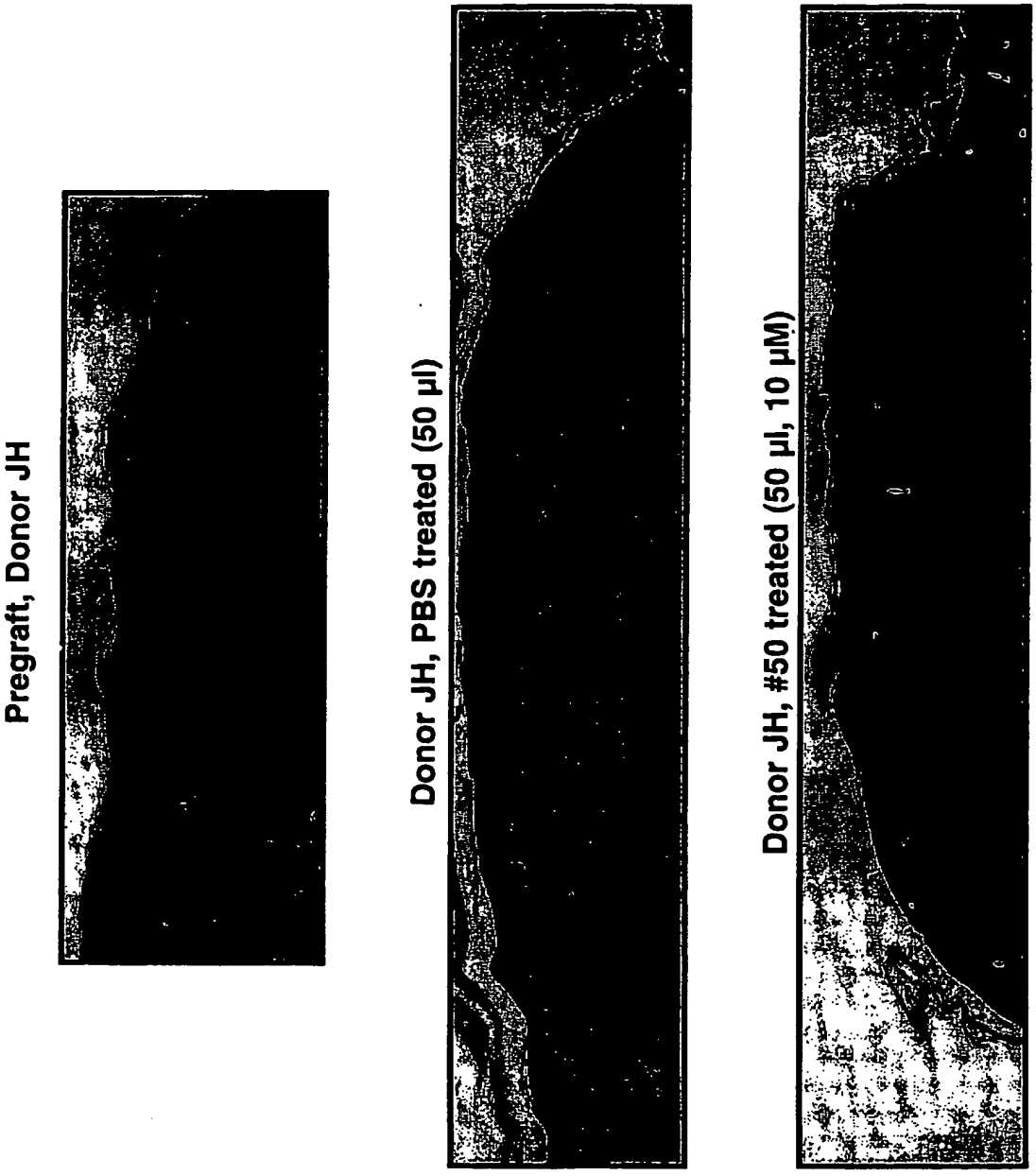

Pregraft, Donor JH
Donor JH, PBS treated (50 µl)
Donor JH, #50 treated (50 µl, 10 µM)

Figure 18a

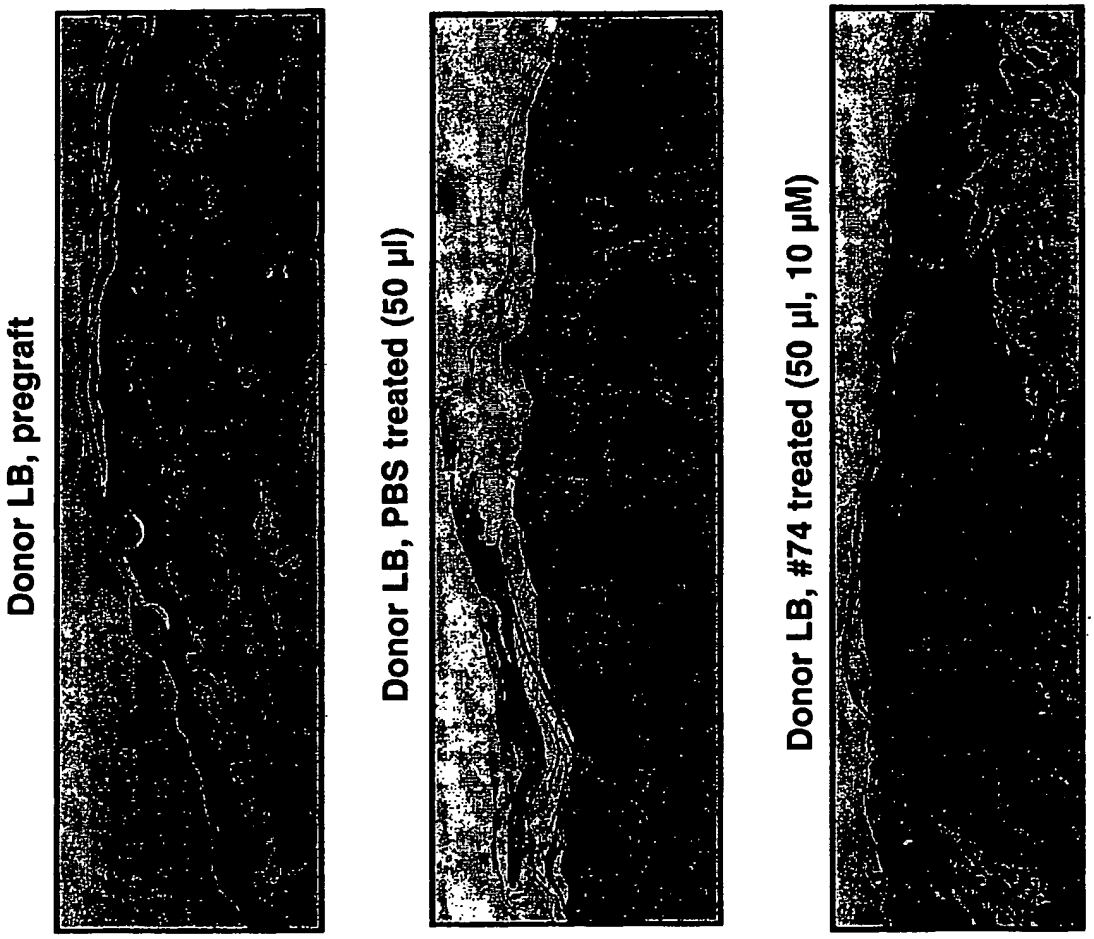

Donor LB, pregraft
Donor LB, PBS treated (50 µl)
Donor LB, #74 treated (50 µl, 10 µM)

Figure 18b

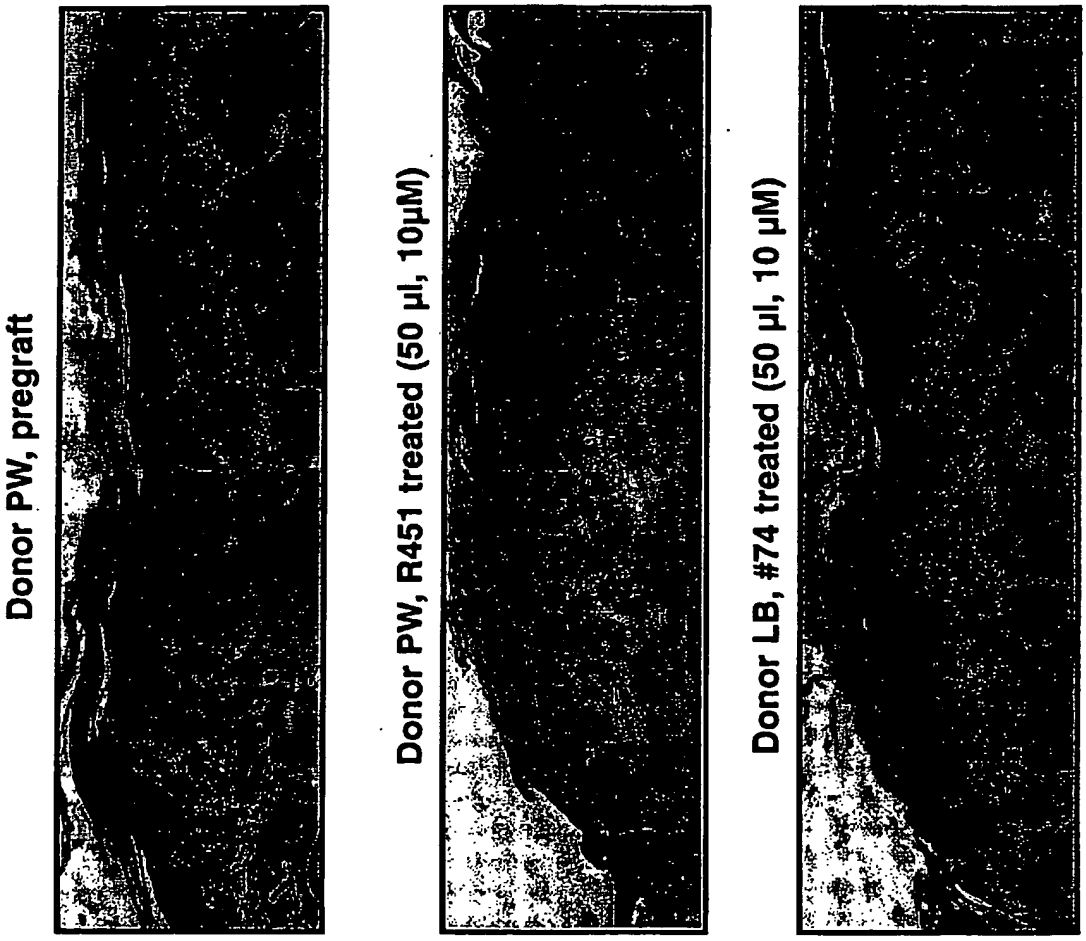

Donor PW, pregraft
Donor PW, R451 treated (50 µl, 10µM)
Donor LB, #74 treated (50 µl, 10 µM)

Figure 18c

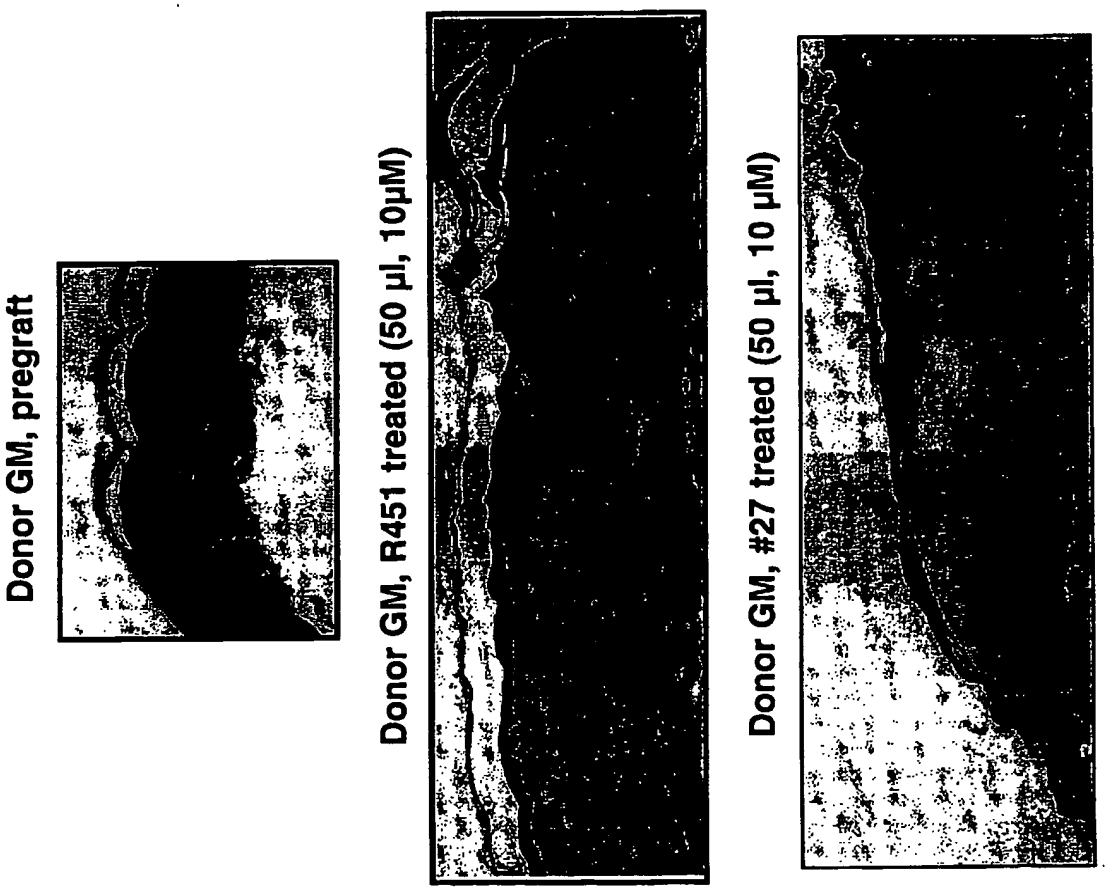
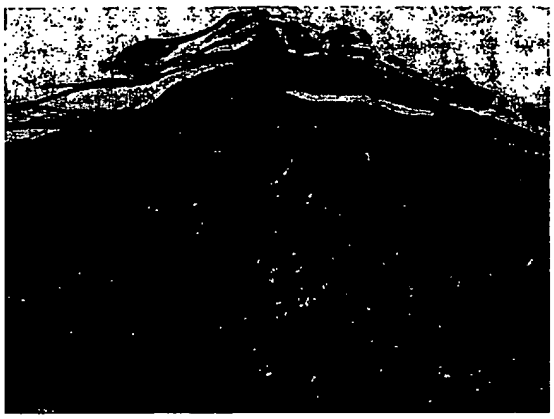
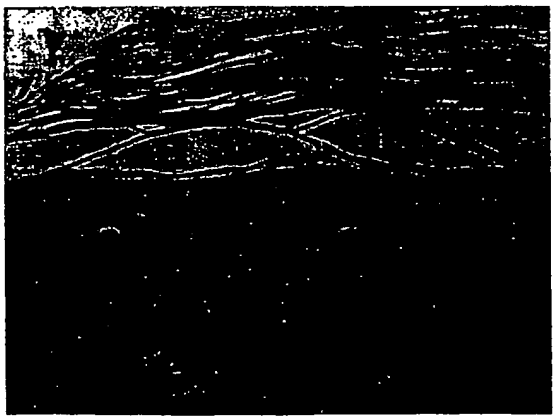

Donor GM, pregraft
Donor GM, R451 treated (50 µl, 10µM)
Donor GM, #27 treated (50 µl, 10 µM)

Figure 18d

Donor JH Pregraft



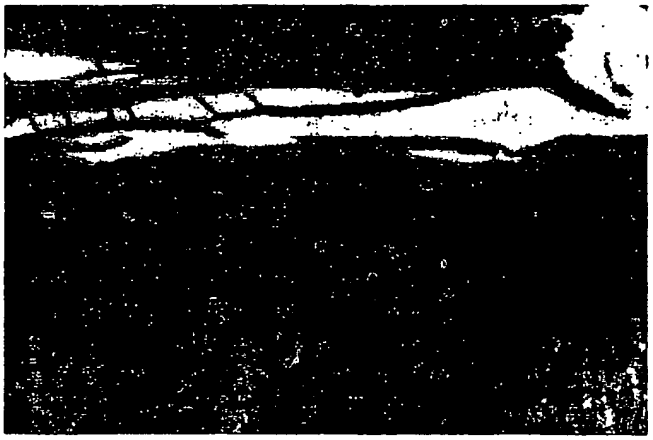
Donor JH PBS treated 50ul



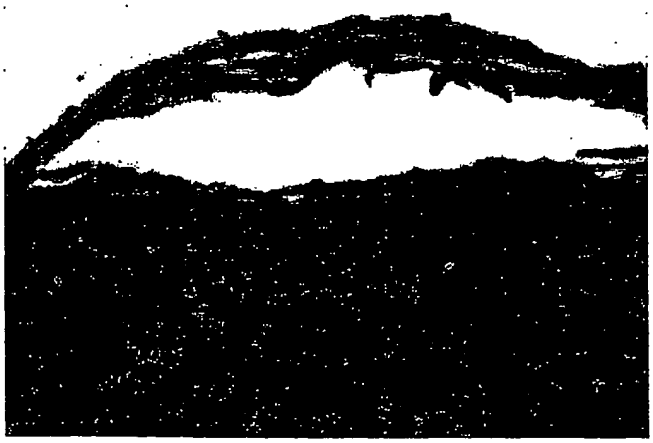
Donor JH # 50 treated 50ul, 10uM

Figure 19a

Donor LB Pregraft

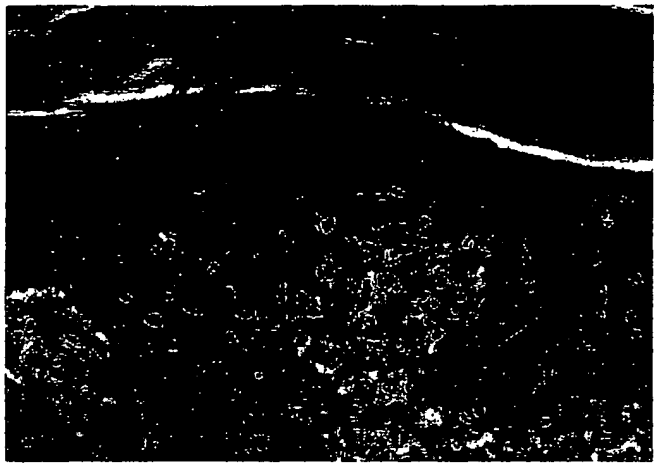


Donor LB PBS treated 50ul

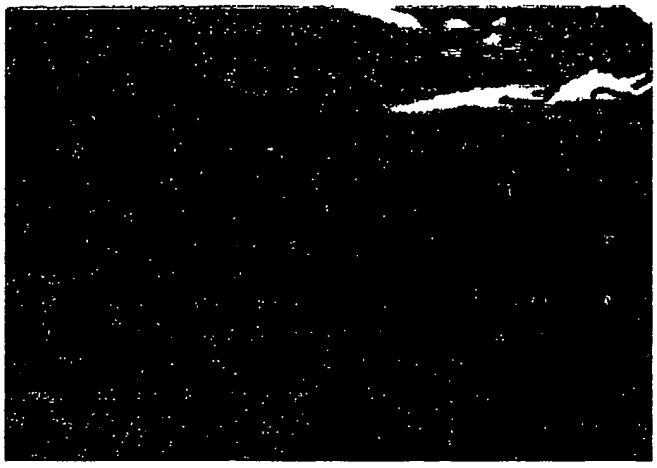


Donor LB # 74 treated 50ul, 10uM

Figure 19b



Donor PW Pregraft



Donor PW R451 treated 50ul, 10um

Donor PW # 74 treated 50ul, 10uM

Figure 19c

Donor GM Pregraft

Donor GM R451 treated 50ul, 10um

Donor GM # 27 treated 50ul, 10uM

Figure 19d

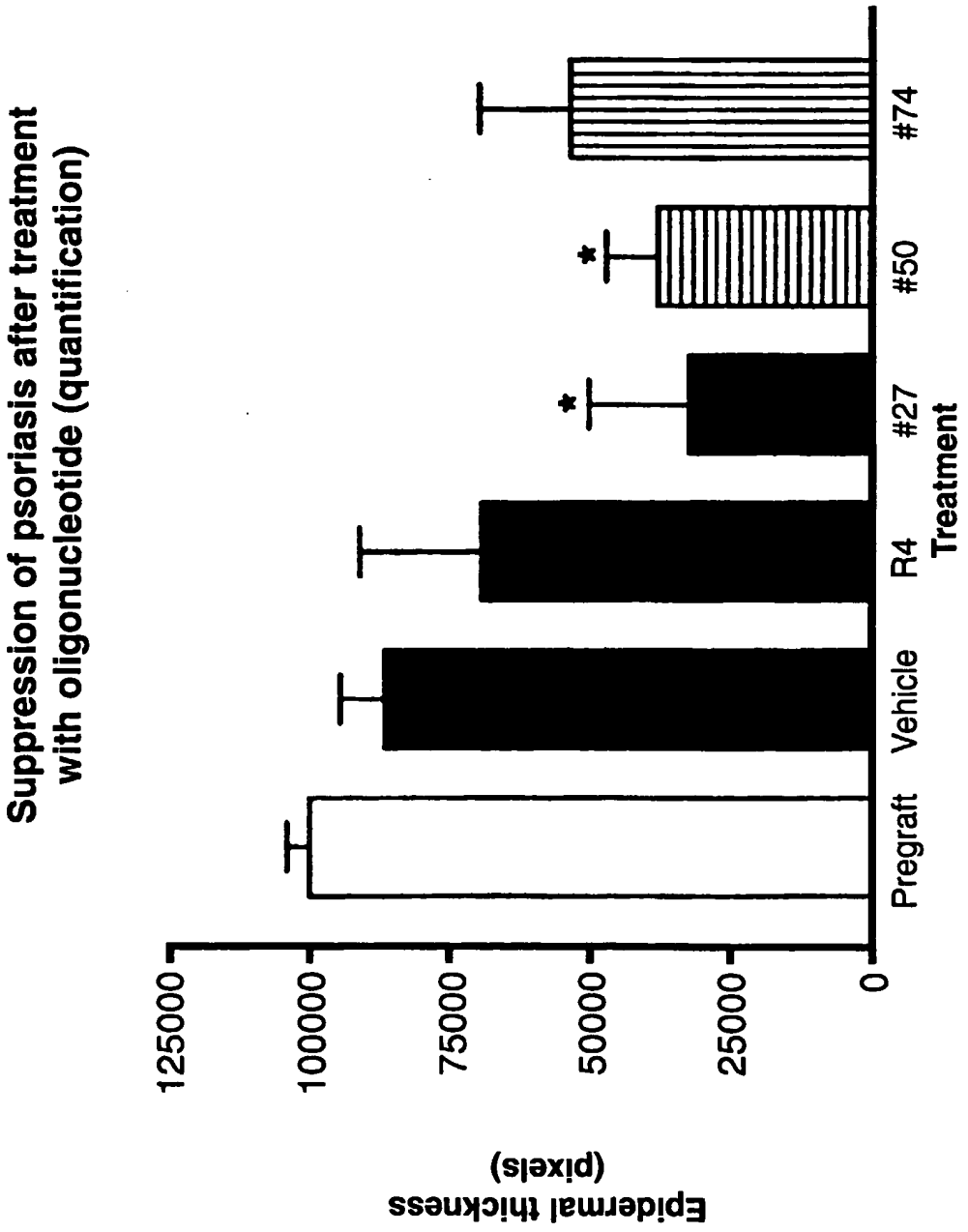

Suppression of psoriasis after treatment with oligonucleotide (quantification)
Epidermal thickness (pixels)
125000
100000
75000
50000
25000
0
Pregraft
Vehicle
R4
#27
#50
#74
Treatment
*
*

Figure 20

αhKi-67

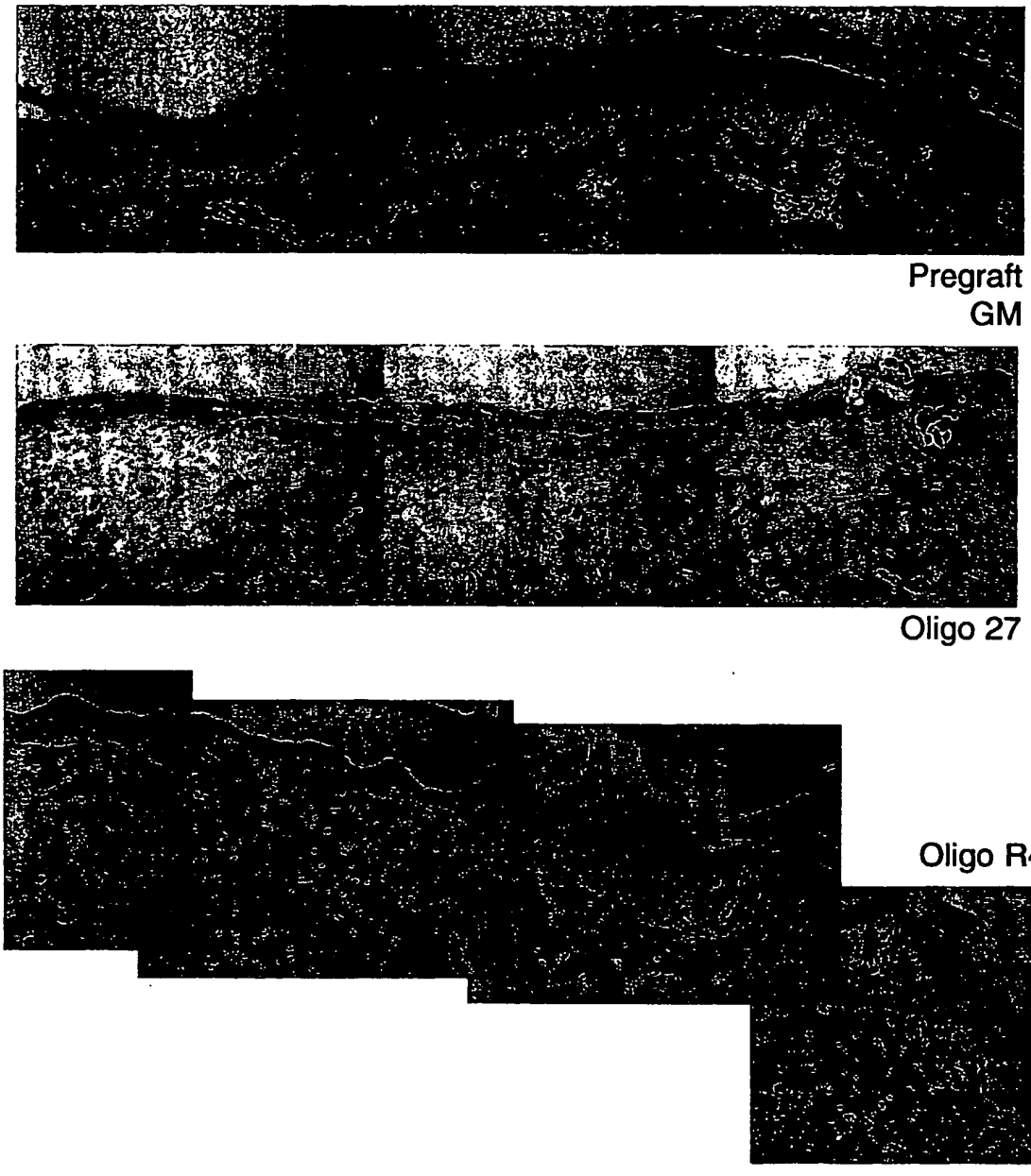



Figure 21

**Penetration of oligonucleotide into human skin after topical treatment**

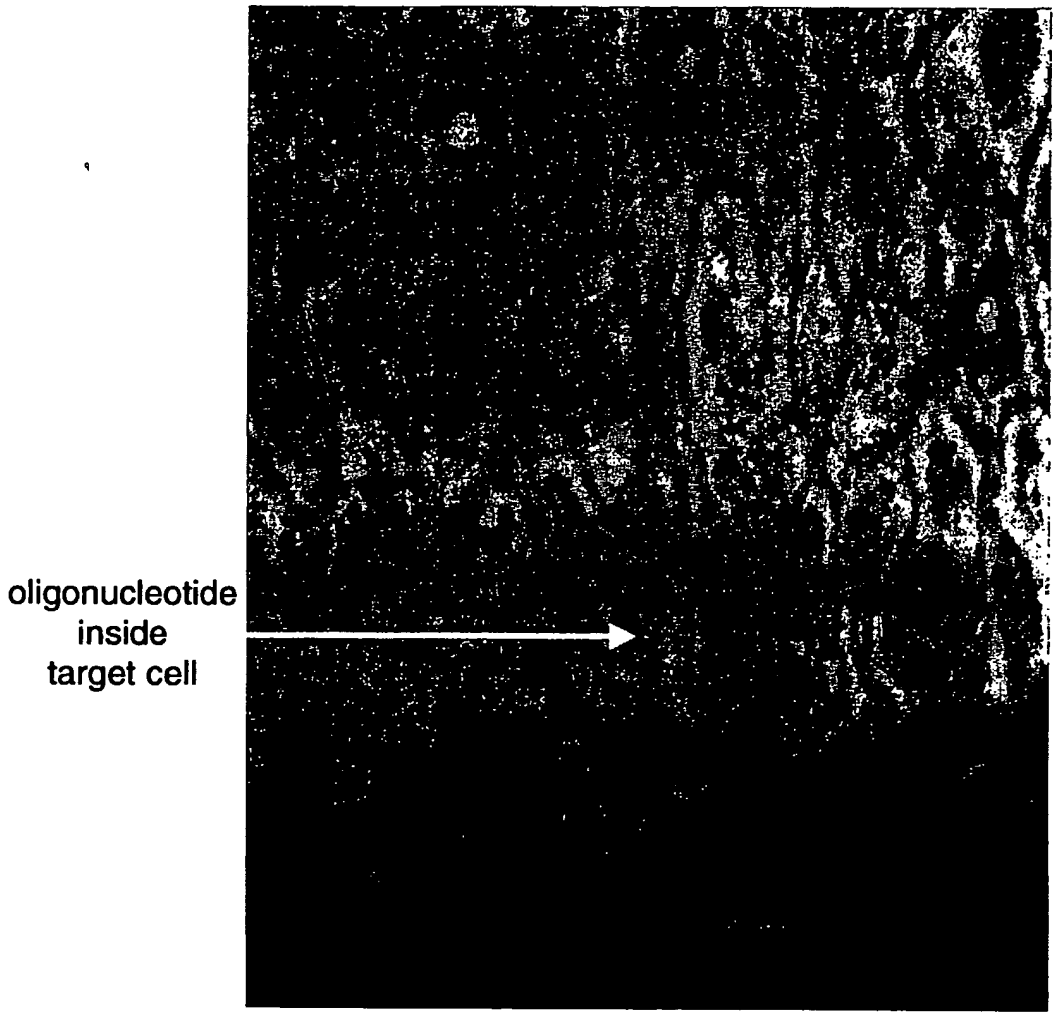



Figure 22

Penetration of oligonucleotide into human skin after topical gel formulation

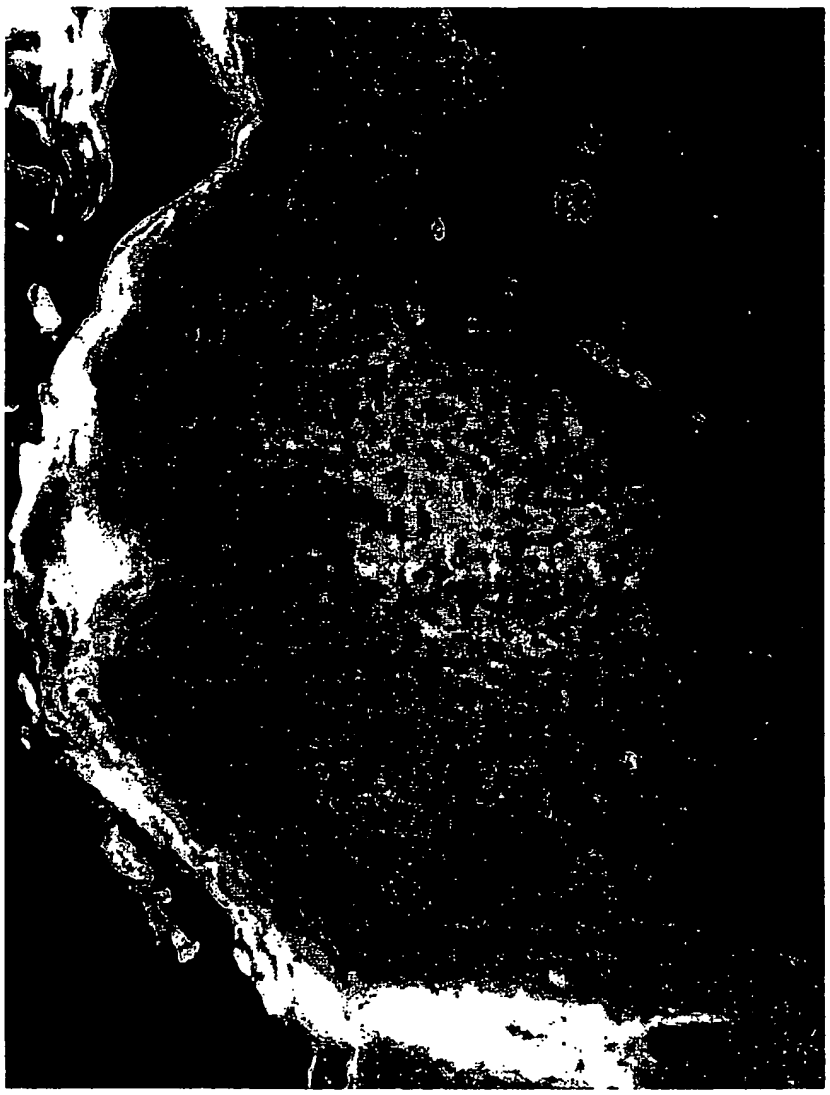


Figure 23

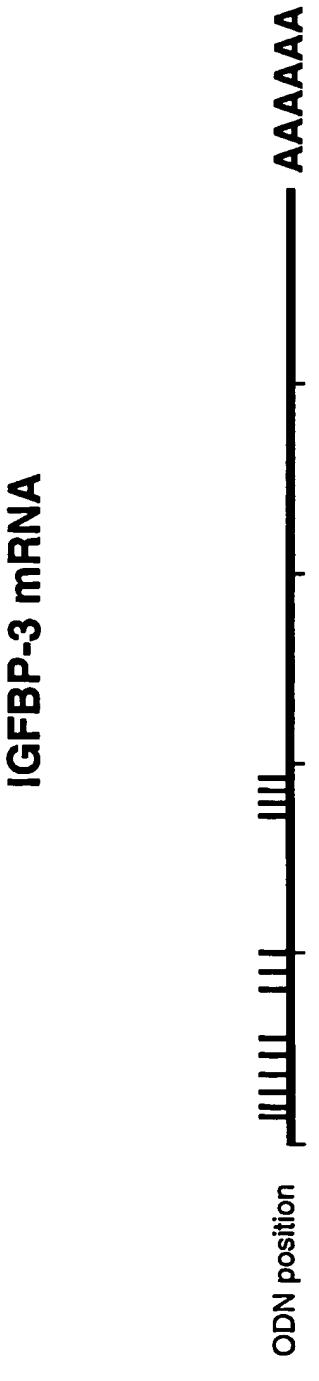

IGFBP-3 mRNA
AAAAAA
2000
1000
0
ODN position
IGFBP-3 protein
• Position of the 13 tested ODNs (I)
• mRNA transcript length = 2.5 Kb
• coding sequence 133-1009

Figure 24

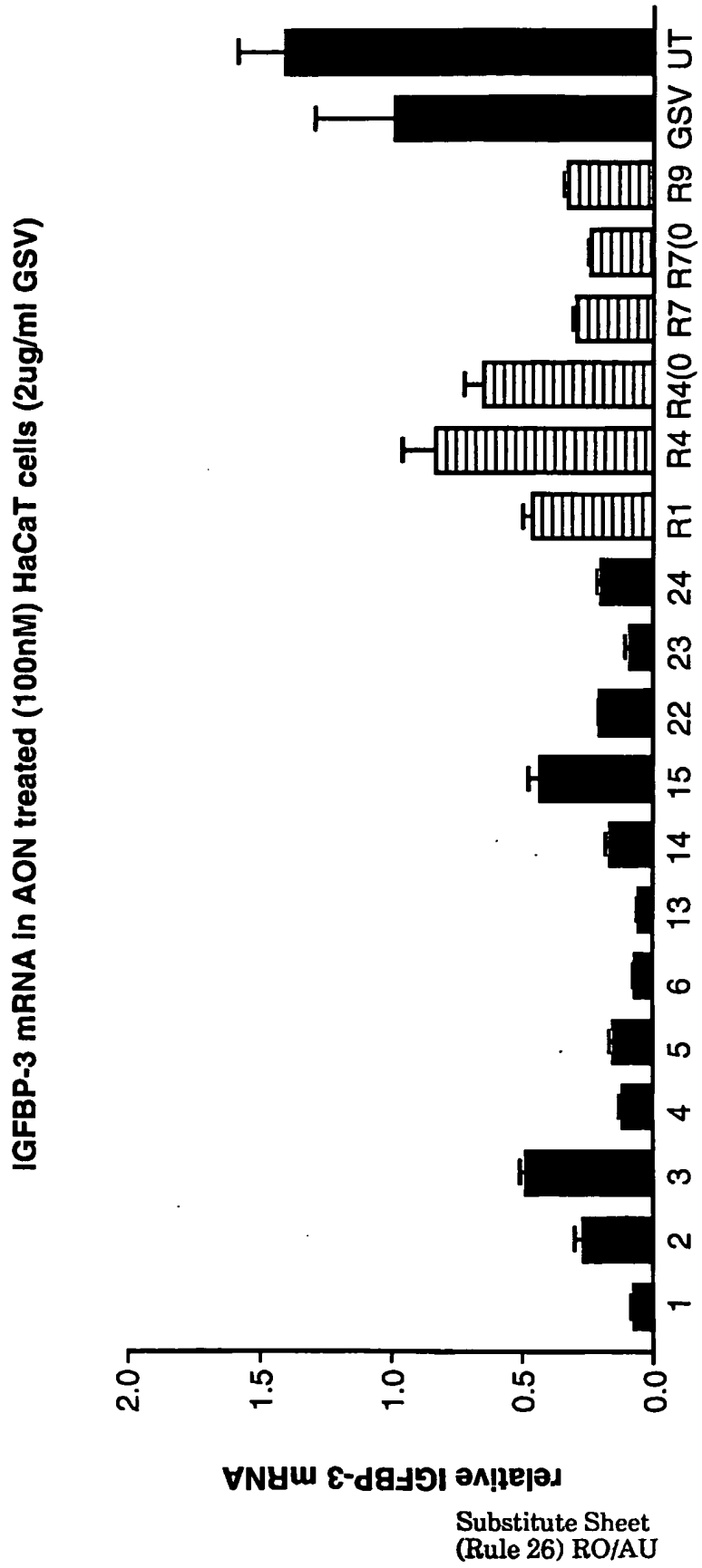

IGFBP-3 mRNA in AON treated (100nM) HaCaT cells (2ug/ml GSV)
relative IGFBP-3 mRNA
2.0
1.5
1.0
0.5
0.0
1
2
3
4
5
6
13
14
15
22
23
24
R1
R4
R4(0
R7
R7(0
R9
GSV
UT
Treatment

Figure 25a

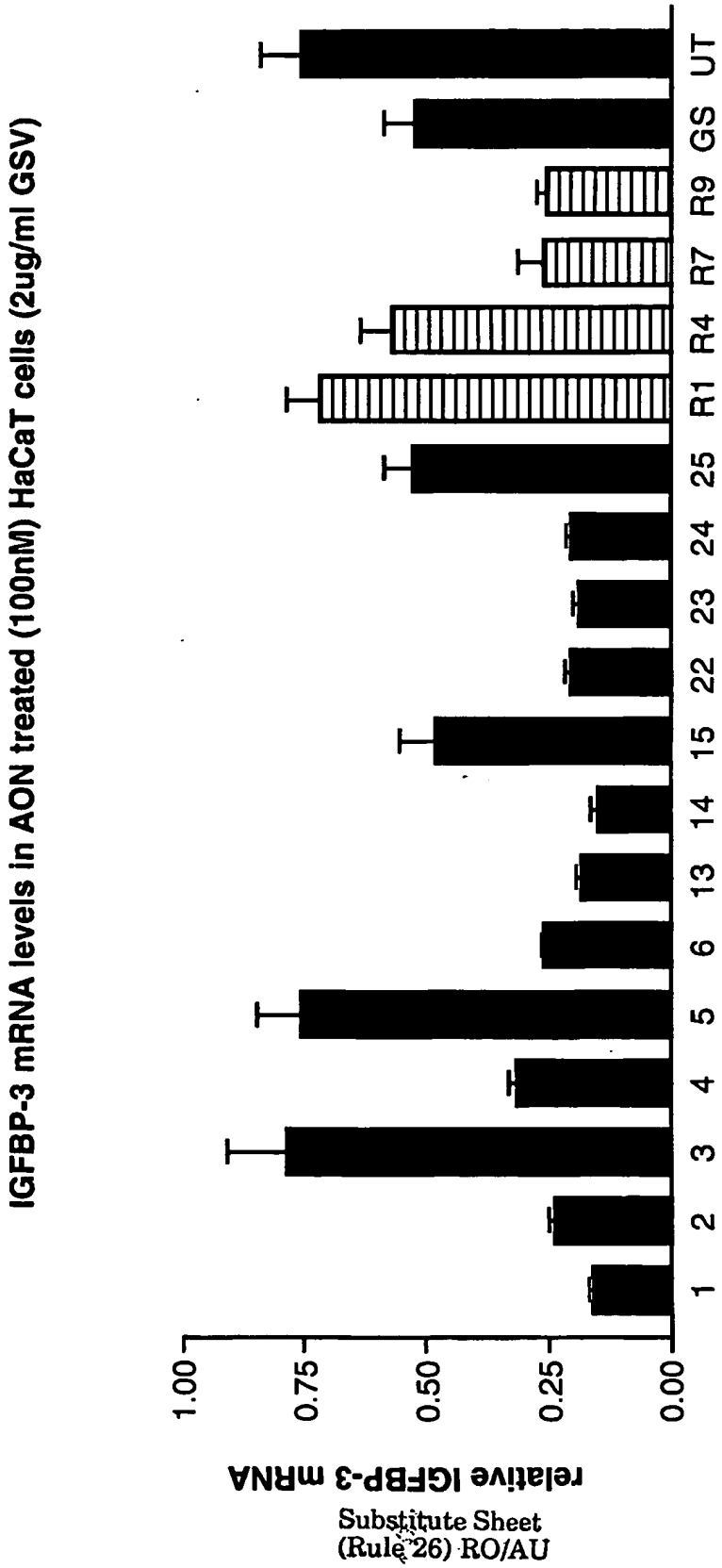

IGFBP-3 mRNA levels in AON treated (100nM) HaCaT cells (2ug/ml GSV)
relative IGFBP-3 mRNA
1.00
0.75
0.50
0.25
0.00
1
2
3
4
5
6
13
14
15
22
23
24
25
R1
R4
R7
R9
GS
UT
Treatment

Figure 25b

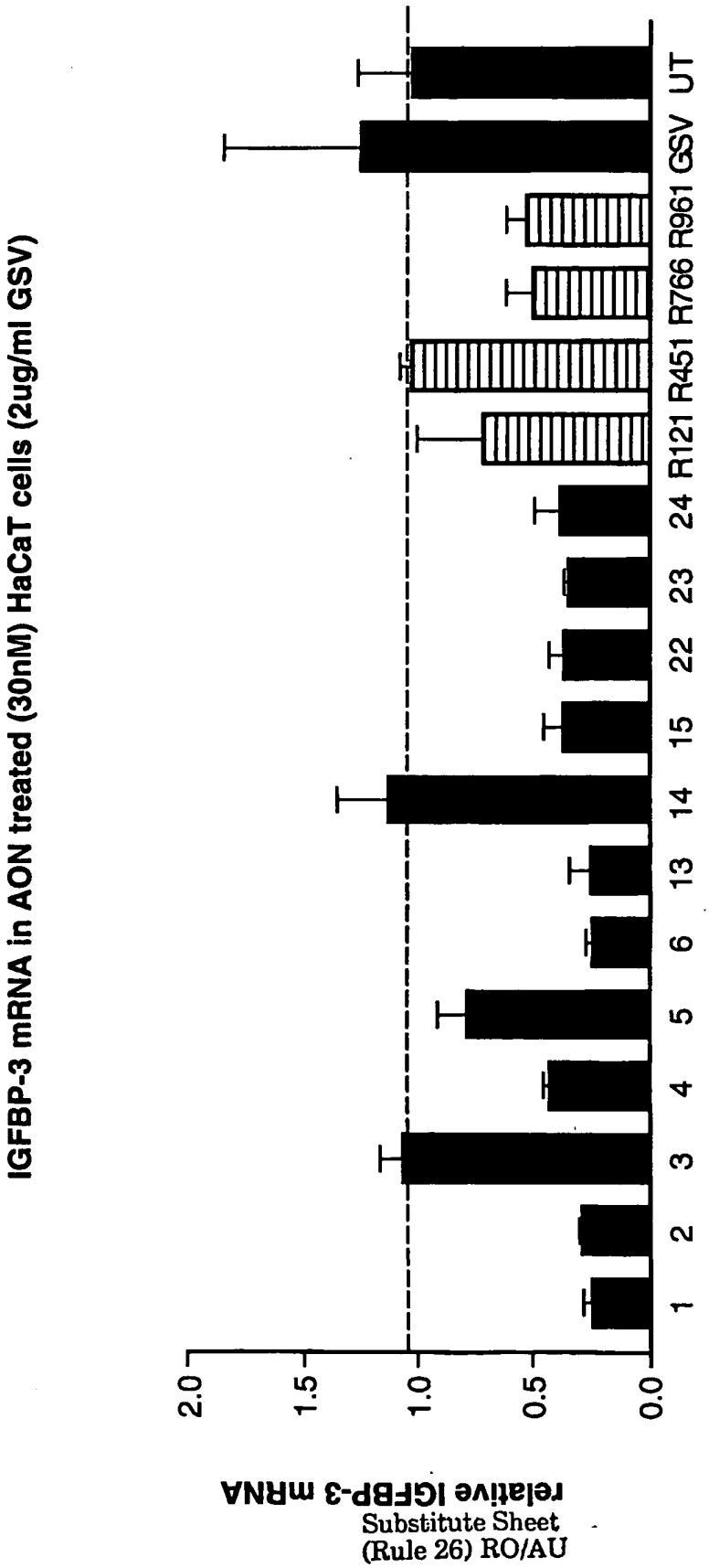

IGFBP-3 mRNA in AON treated (30nM) HaCaT cells (2ug/ml GSV)
relative IGFBP-3 mRNA
2.0
1.5
1.0
0.5
0.0
1
2
3
4
5
6
13
14
15
22
23
24
R121
R451
R766
R961
GSV
UT
Treatment

Figure 25c

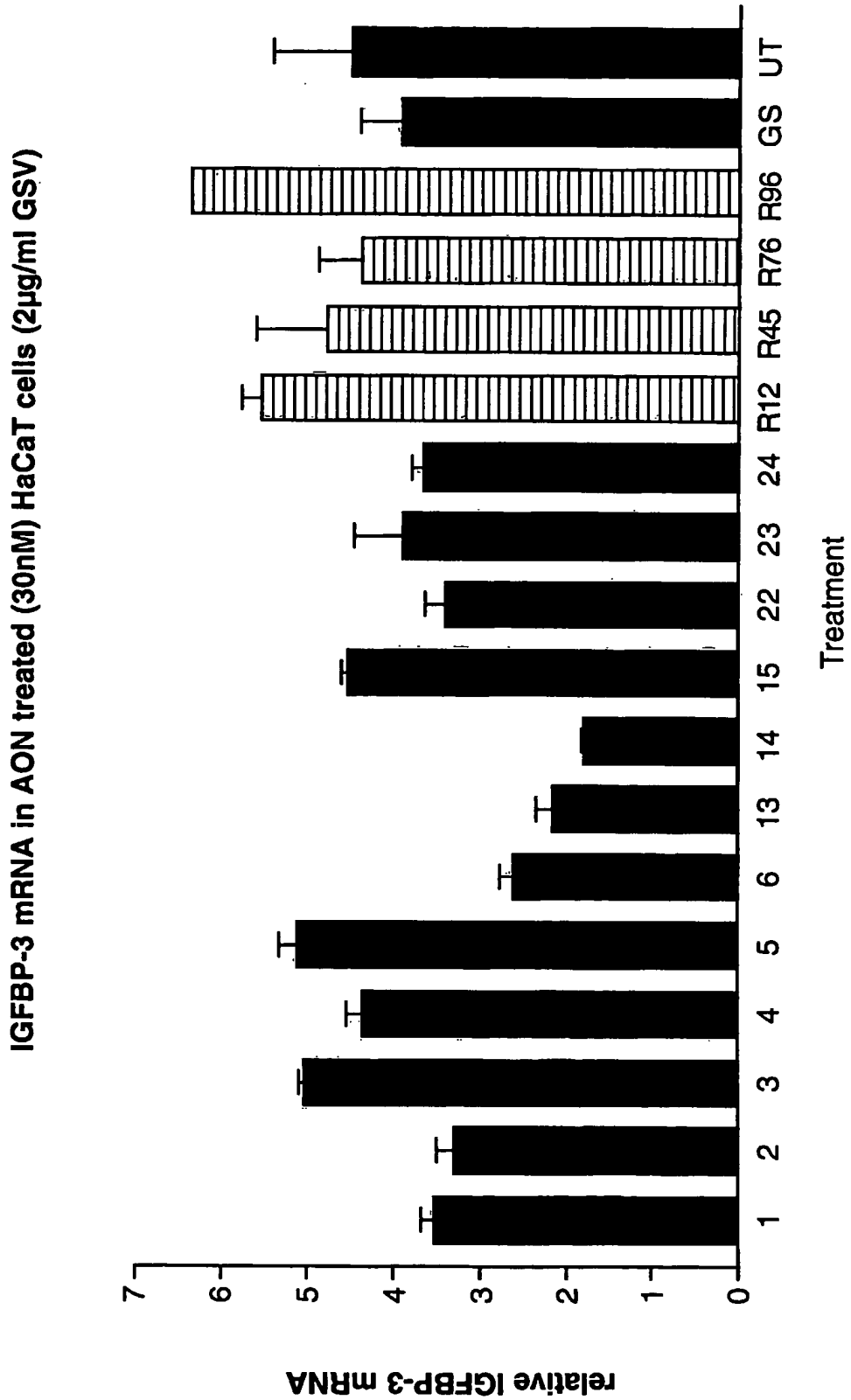

IGFBP-3 mRNA in AON treated (30nM) HaCaT cells (2µg/ml GSV)
relative IGFBP-3 mRNA
0
1
2
3
4
5
6
7
1
2
3
4
5
6
13
14
15
22
23
24
R12
R45
R76
R96
GS
UT
Treatment

Figure 25d

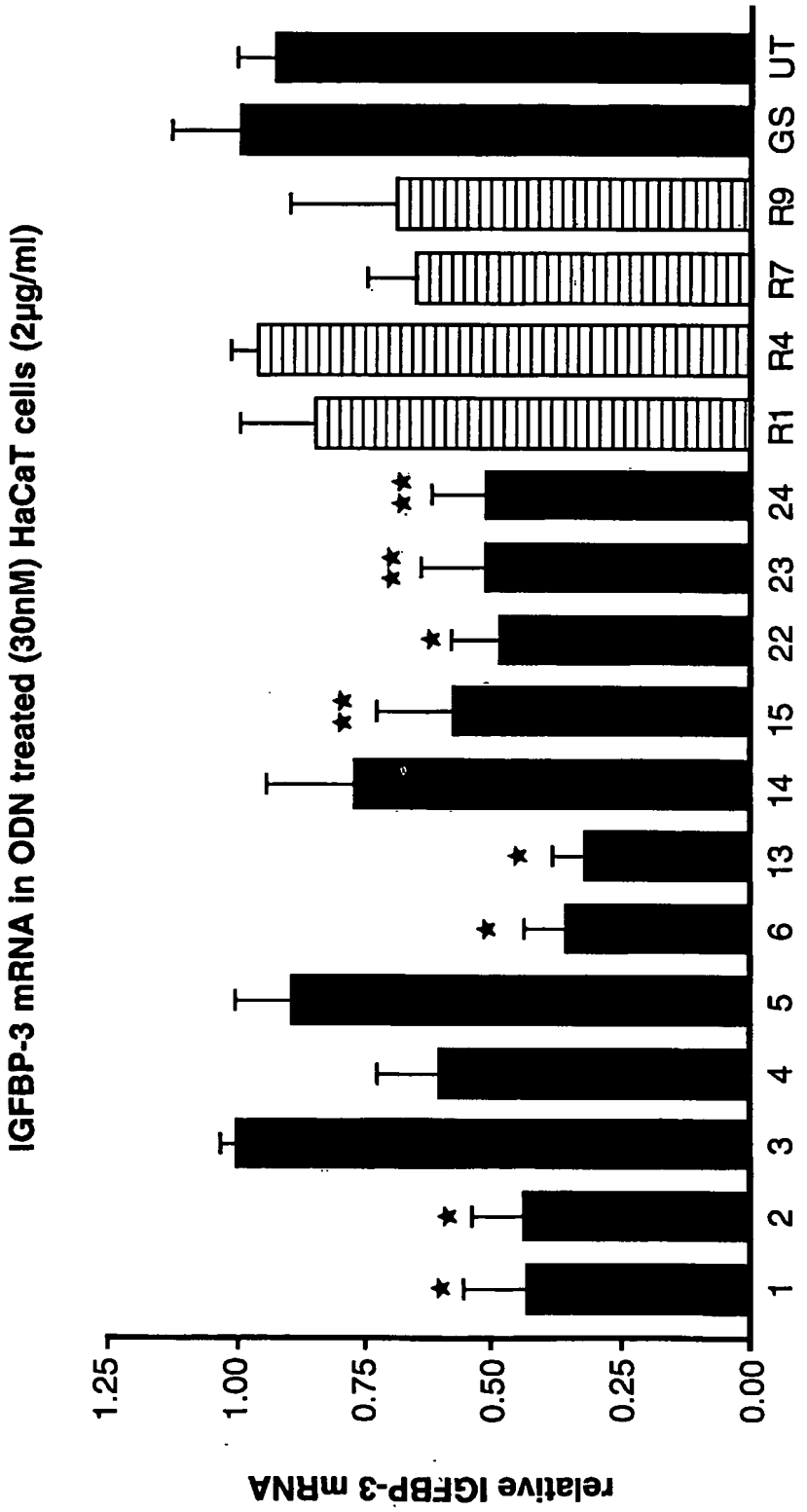

IGFBP-3 mRNA in ODN treated (30nM) HaCaT cells (2µg/ml)
relative IGFBP-3 mRNA
1.25
1.00
0.75
0.50
0.25
0.00
1
2
3
4
5
6
13
14
15
22
23
24
R1
R4
R7
R9
GS
UT
Treatment

Figure 26a

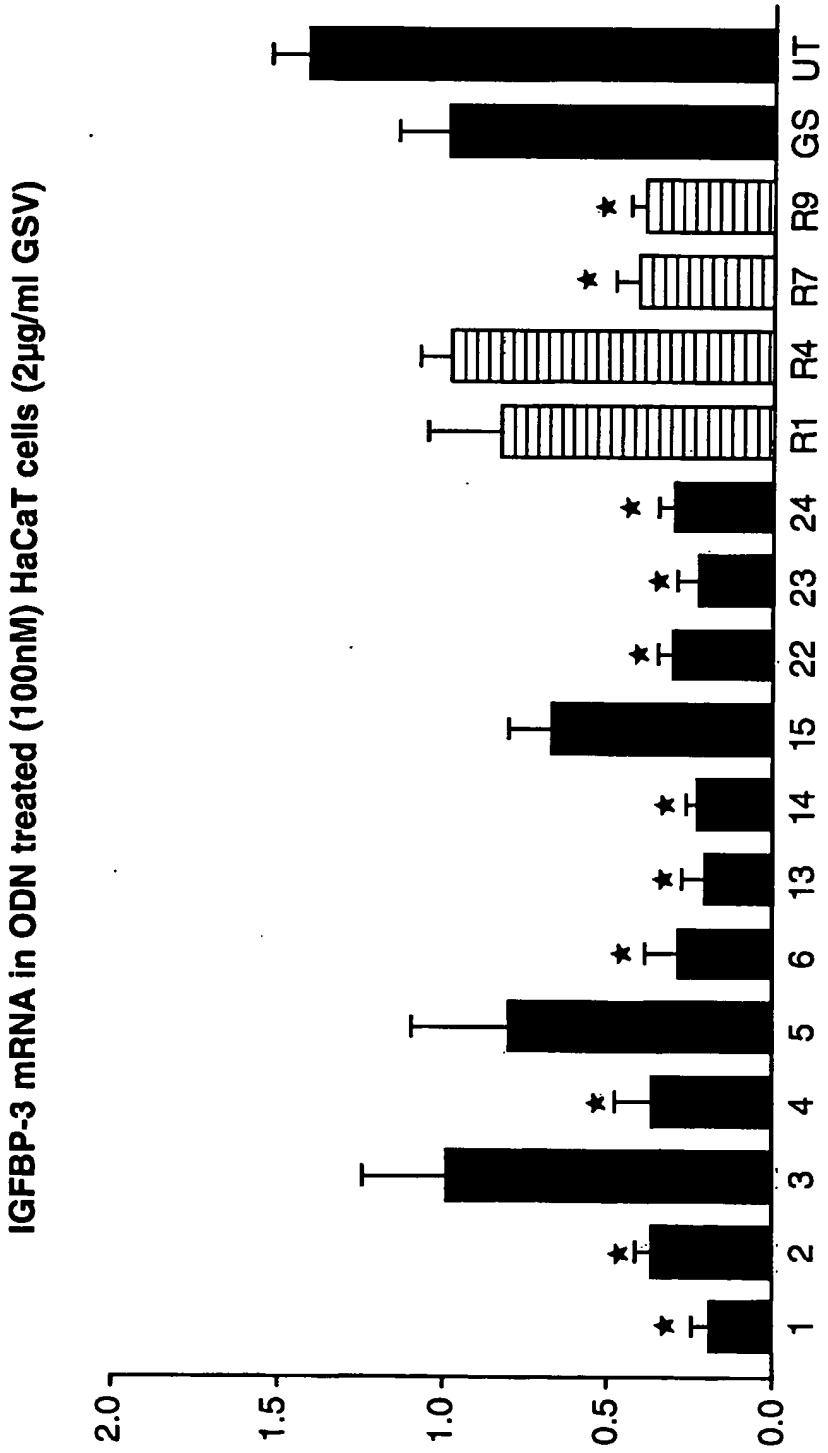

IGFBP-3 mRNA in ODN treated (100nM) HaCaT cells (2µg/ml GSV)
relative IGFBP-3 mRNA
2.0
1.5
1.0
0.5
0.0
1
2
3
4
5
6
13
14
15
22
23
24
R1
R4
R7
R9
GS
UT
Treatment

Figure 26b

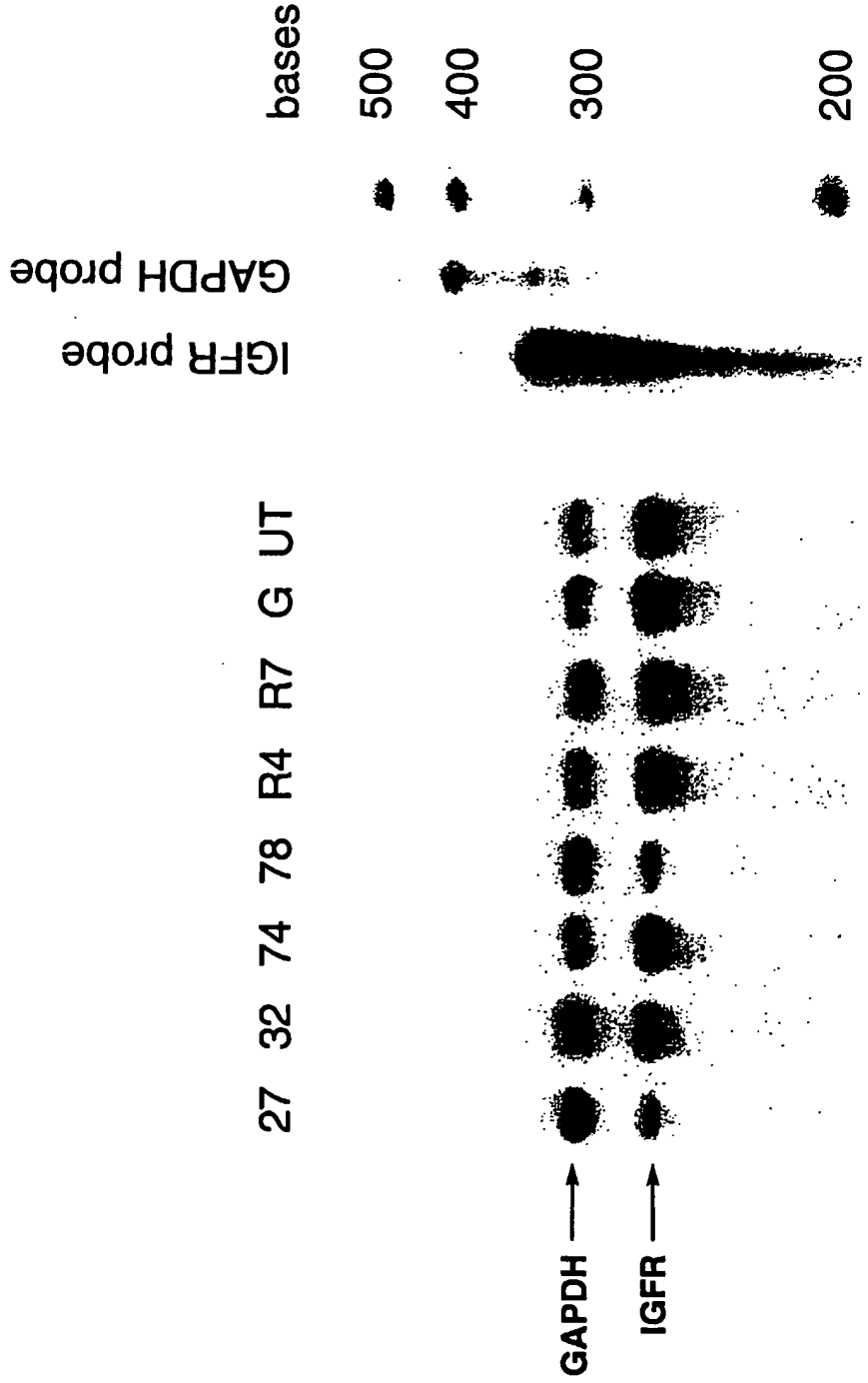

bases
500
400
300
200
GAPDH probe
IGFR probe
27 32 74 78 R4 R7 G UT
GAPDH
IGFR

Figure 27a

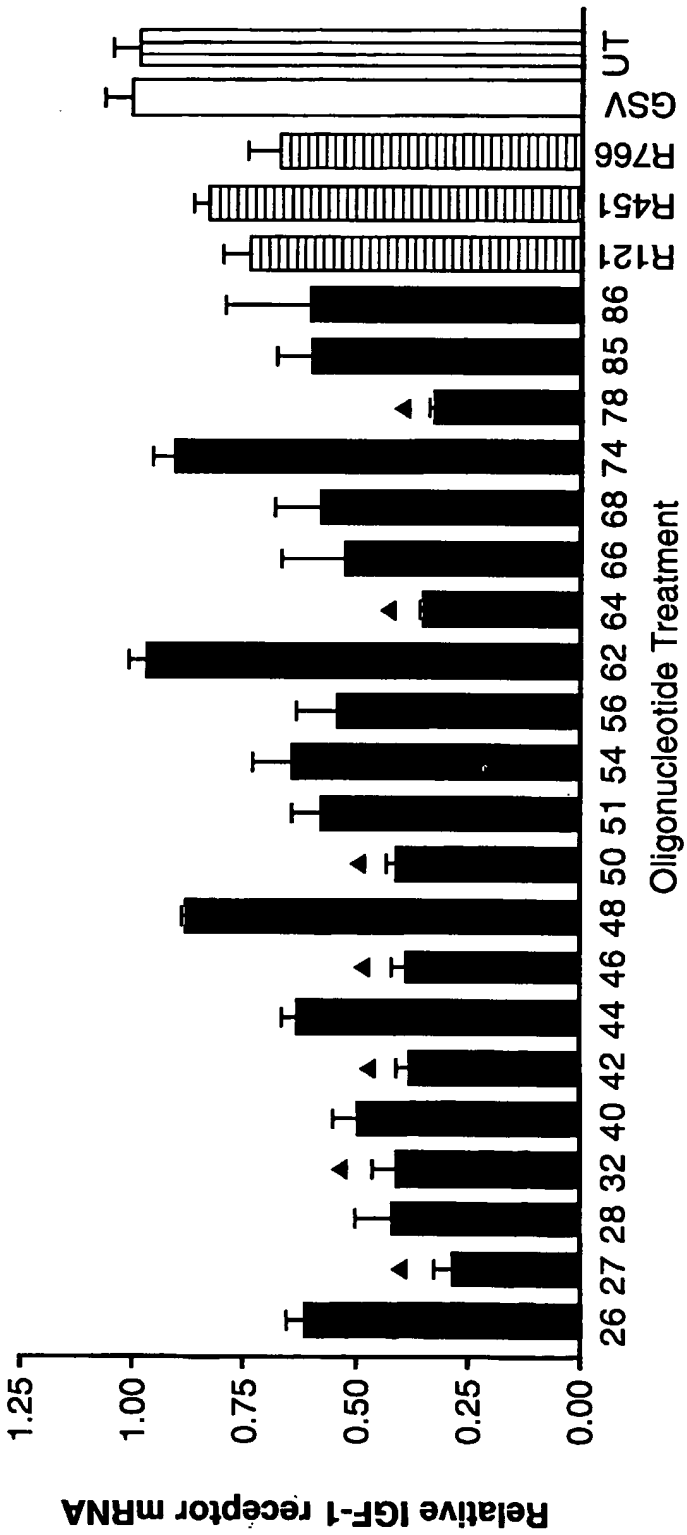

Relative IGF-1 receptor mRNA
1.25
1.00
0.75
0.50
0.25
0.00
26 27 28 32 40 42 44 46 48 50 51 54 56 62 64 66 68 74 78 85 86
R121
R451
R766
GSV
UT
Oligonucleotide Treatment

Figure 27 b

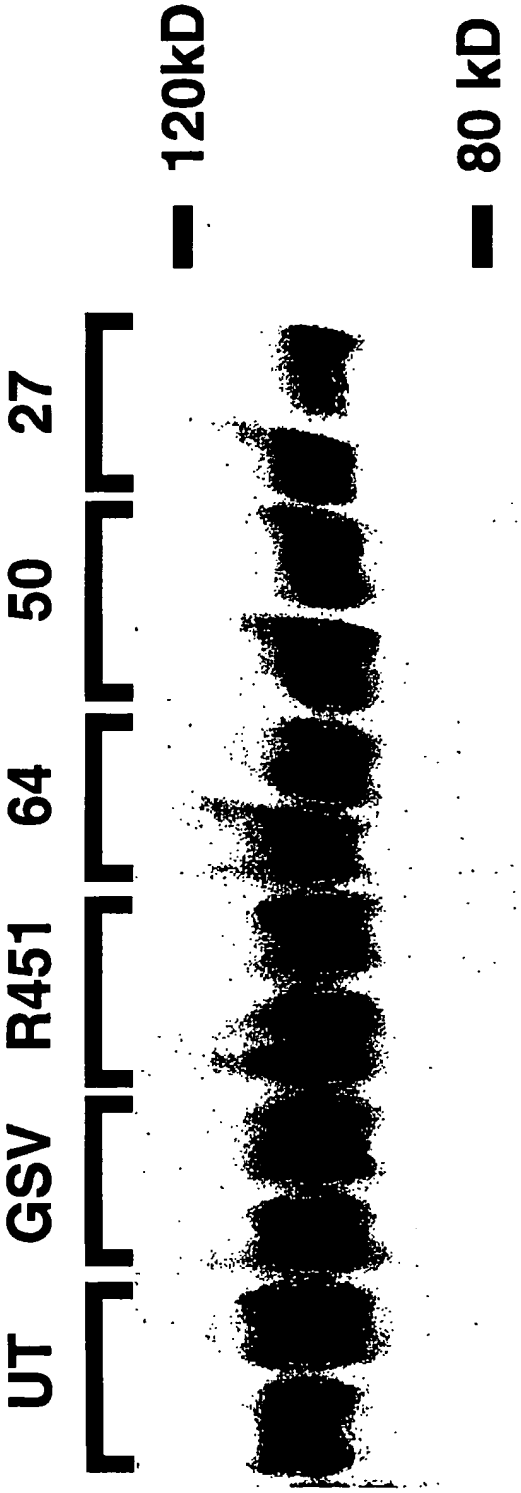



Figure 28a

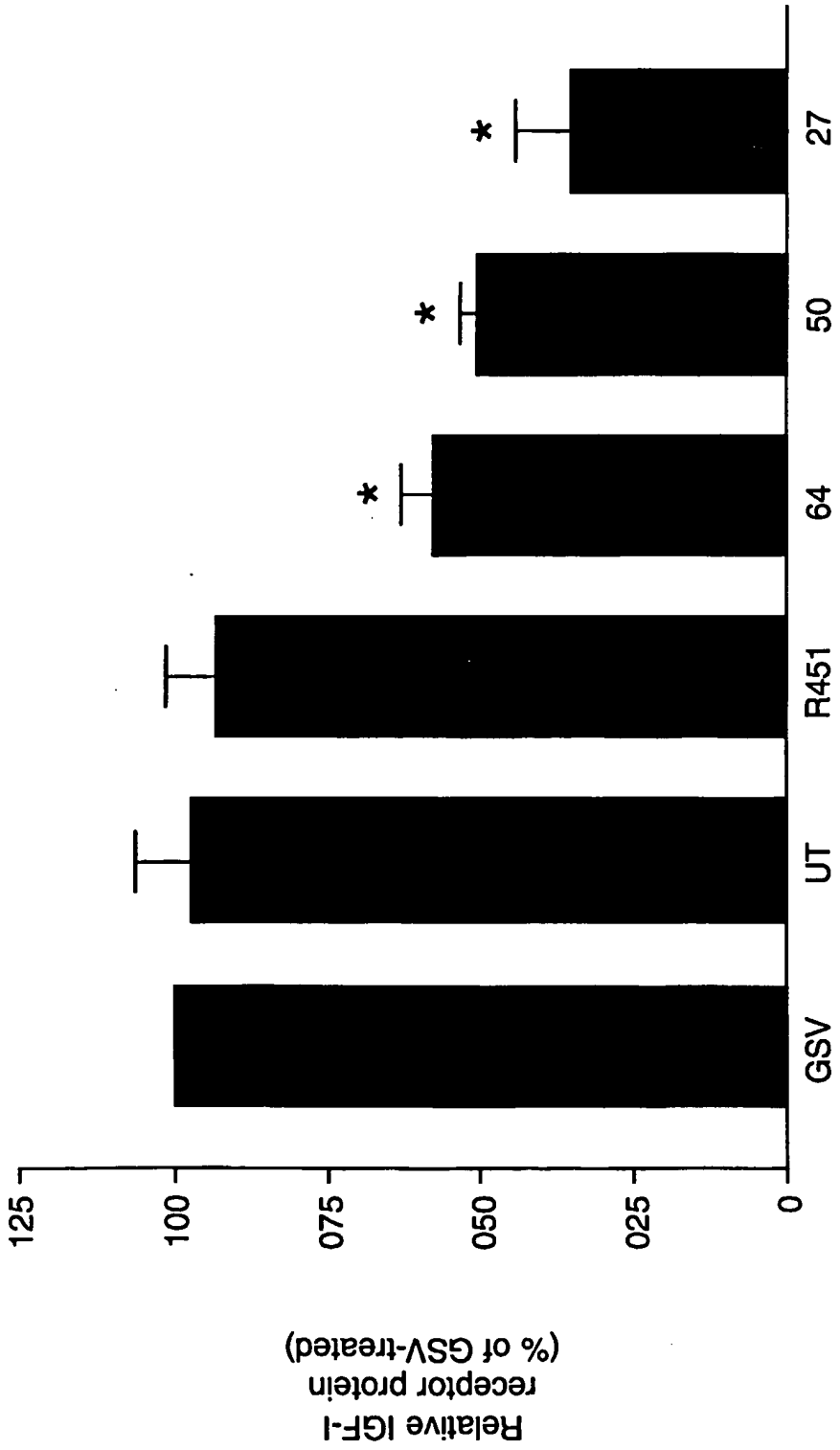

Relative IGF-I
receptor protein
(% of GSV-treated)
125
100
075
050
025
0
GSV
UT
R451
64
50
27
*
*
*

Figure 28b

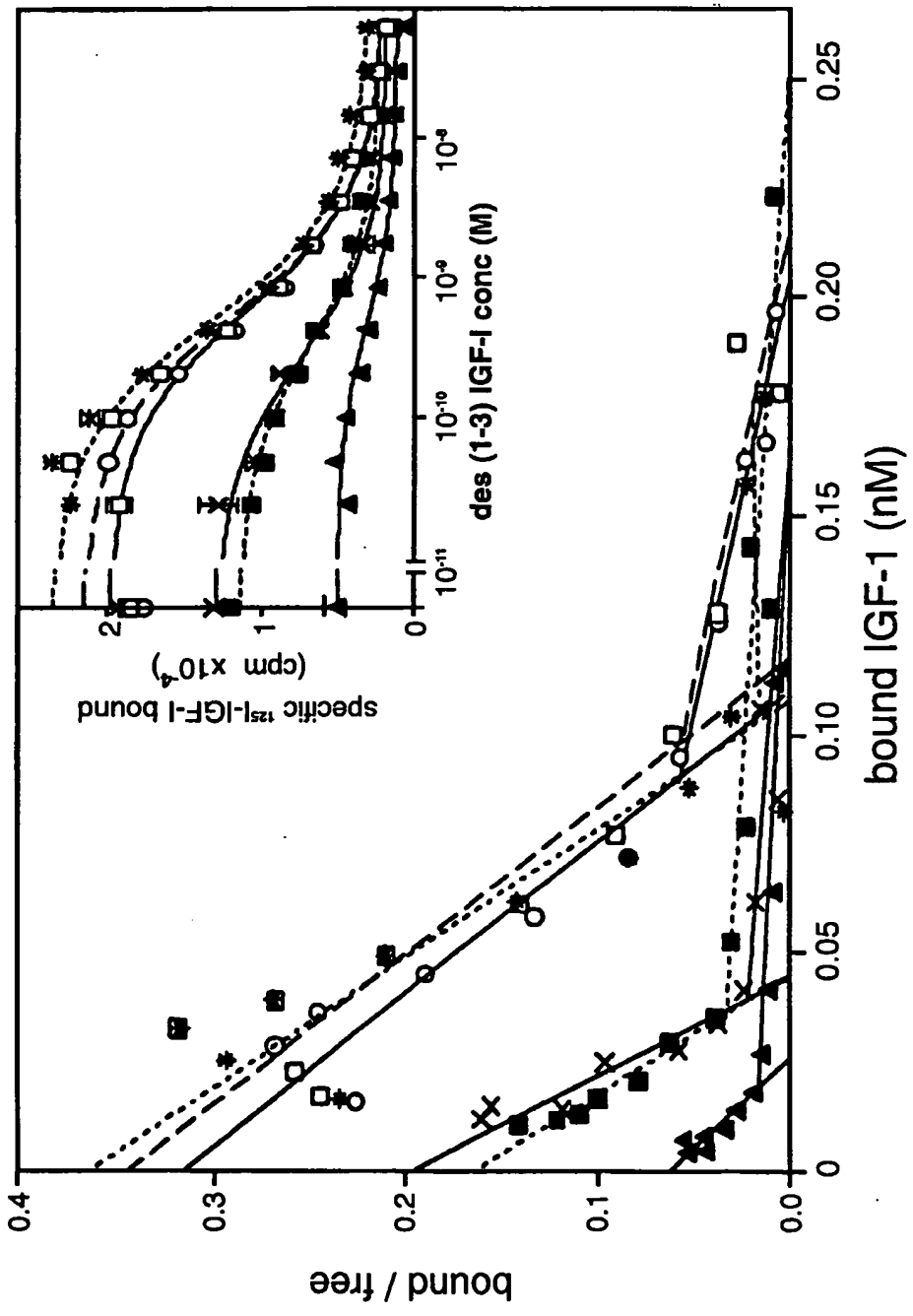

bound / free
0.4
0.3
0.2
0.1
0.0
bound IGF-1 (nM)
0
0.05
0.10
0.15
0.20
0.25
specific $^{125}$I-IGF-I bound
(cpm x10$^{-4}$)
2
1
0
des (1-3) IGF-I conc (M)
$10^{-11}$
$10^{-10}$
$10^{-9}$
$10^{-8}$

Figure 29

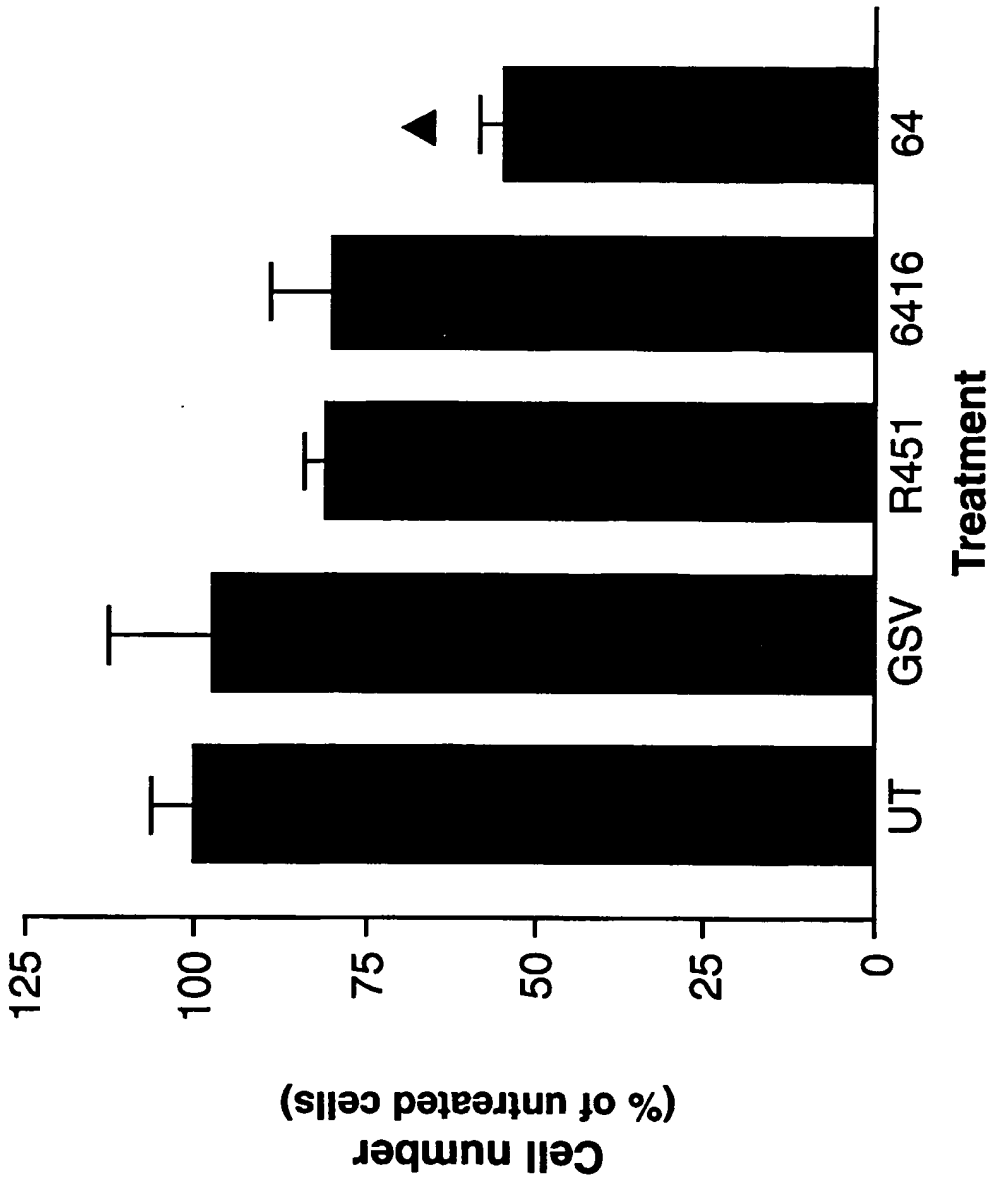

Cell number
(% of untreated cells)
125
100
75
50
25
0
UT
GSV
R451
6416
64
Treatment

Figure 30

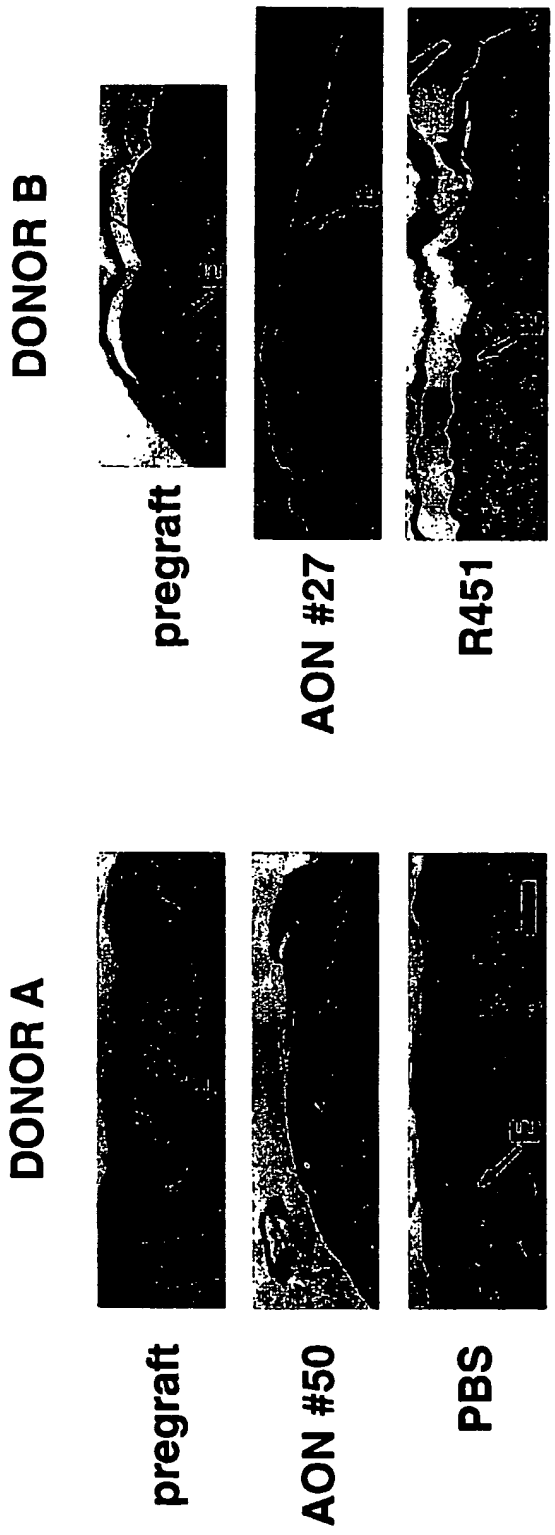



Figure 31a

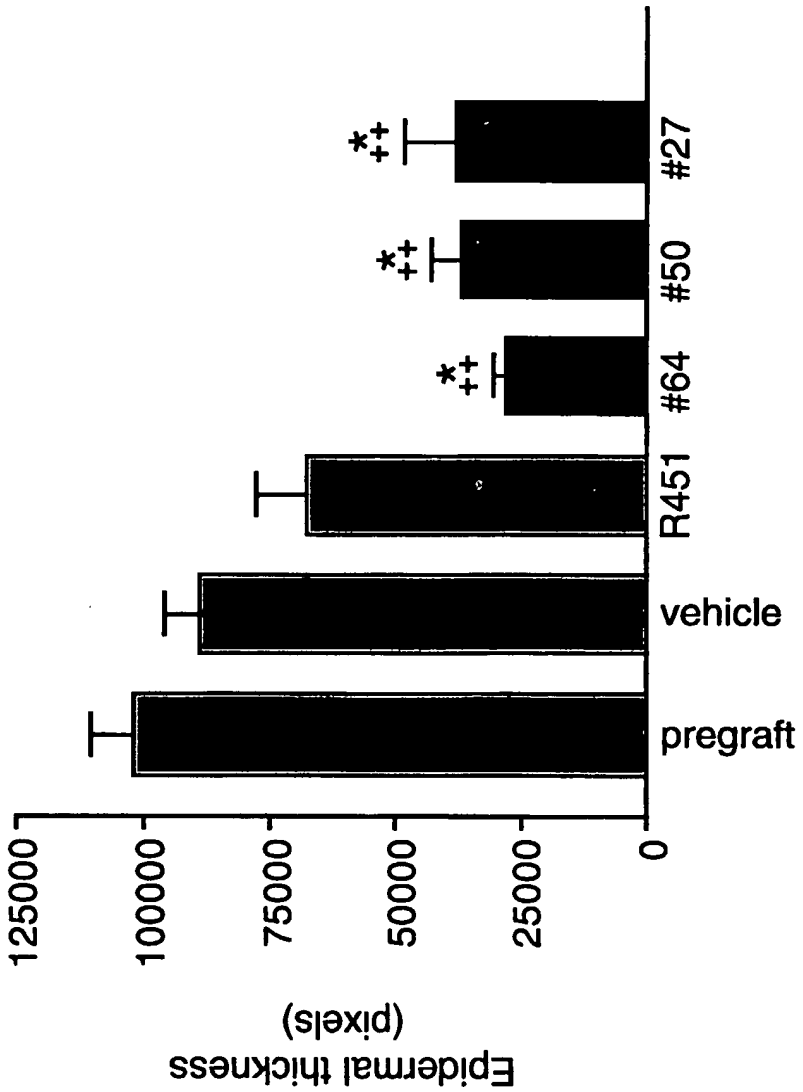

Epidermal thickness
(pixels)
125000
100000
75000
50000
25000
0
pregraft
vehicle
R451
#64
#50
#27
*++
*++
*++
*++

Figure 31b

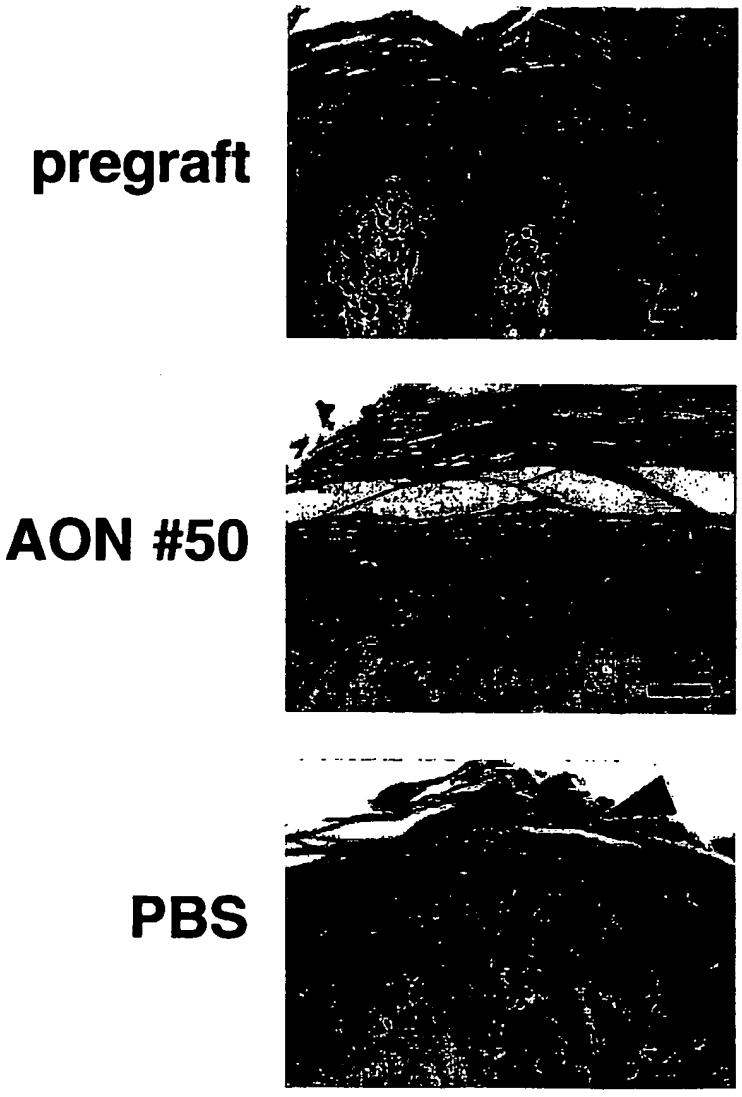
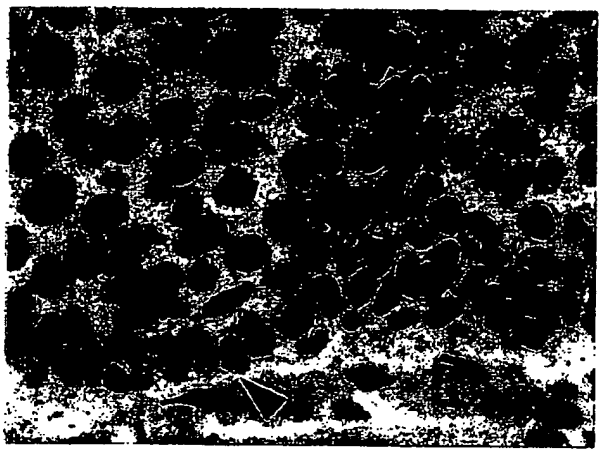



Figure 31c


Figure 32a

pregraft



AON #27

R451

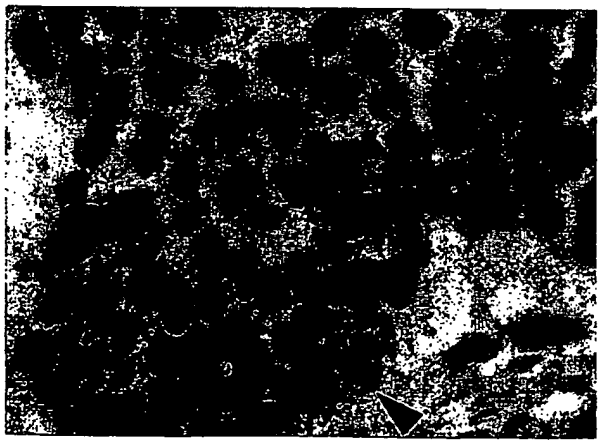


Figure 32b

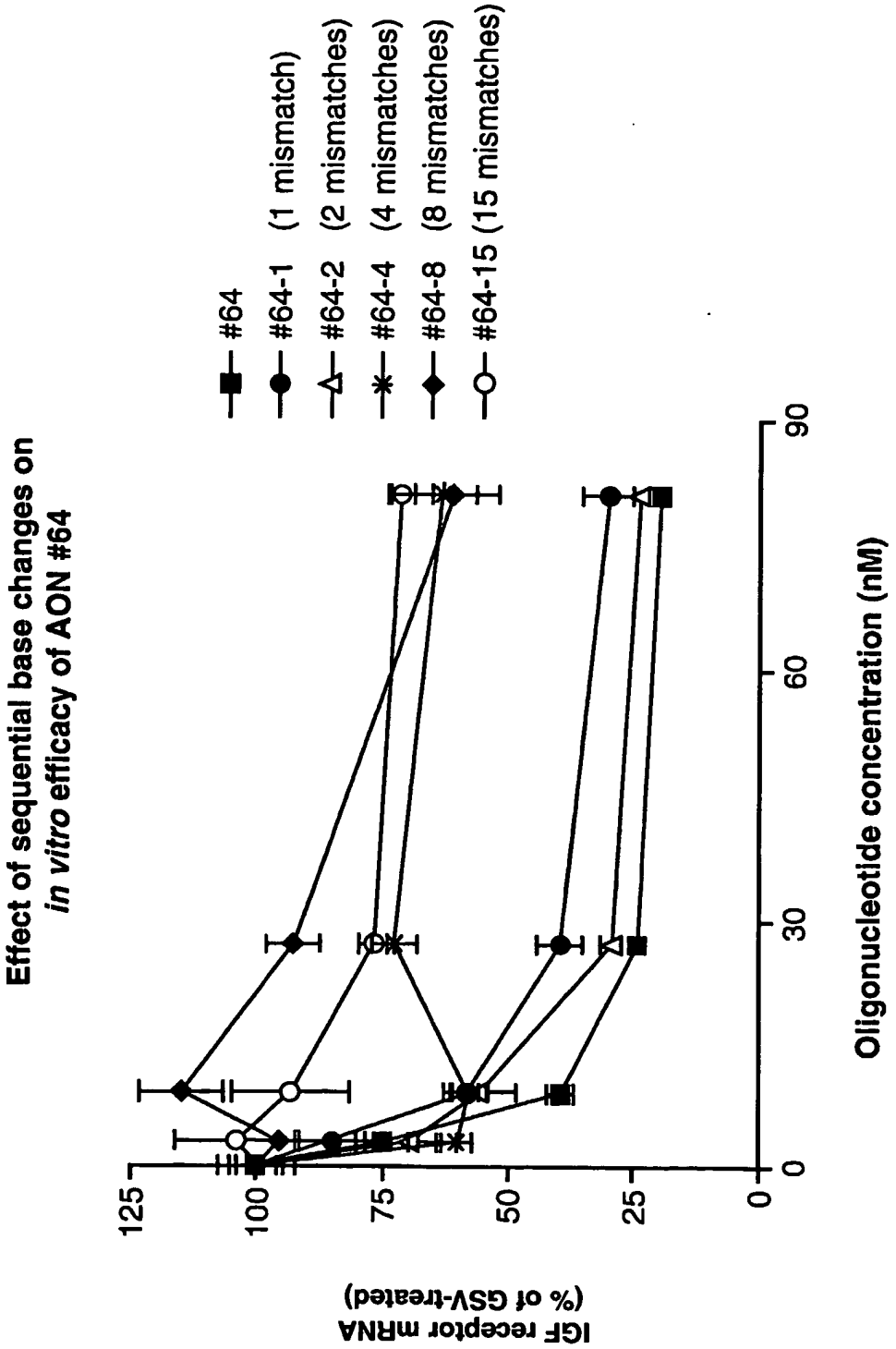

Effect of sequential base changes on
in vitro efficacy of AON #64
#64
#64-1 (1 mismatch)
#64-2 (2 mismatches)
#64-4 (4 mismatches)
#64-8 (8 mismatches)
#64-15 (15 mismatches)
IGF receptor mRNA
(% of GSV-treated)
125
100
75
50
25
0
0
30
60
90
Oligonucleotide concentration (nM)

Figure 33

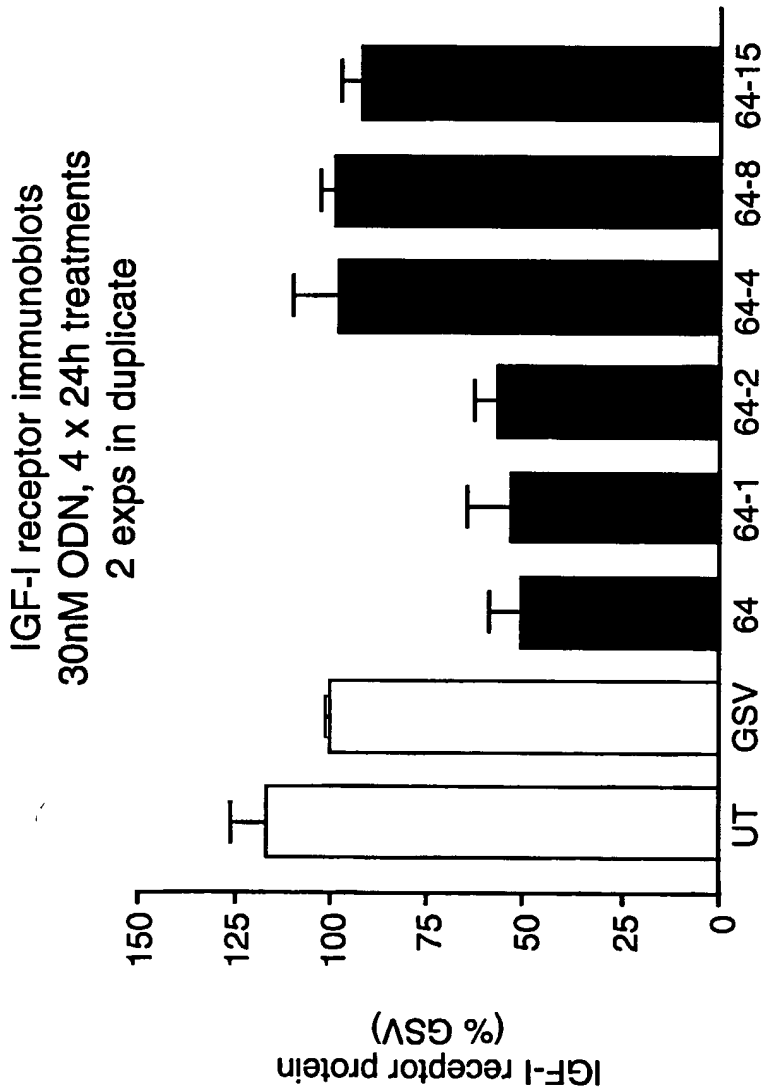

IGF-I receptor immunoblots
30nM ODN, 4 x 24h treatments
2 exps in duplicate
IGF-I receptor protein
(% GSV)
150
125
100
75
50
25
0
UT
GSV
64
64-1
64-2
64-4
64-8
64-15
Treatment

Figure 34

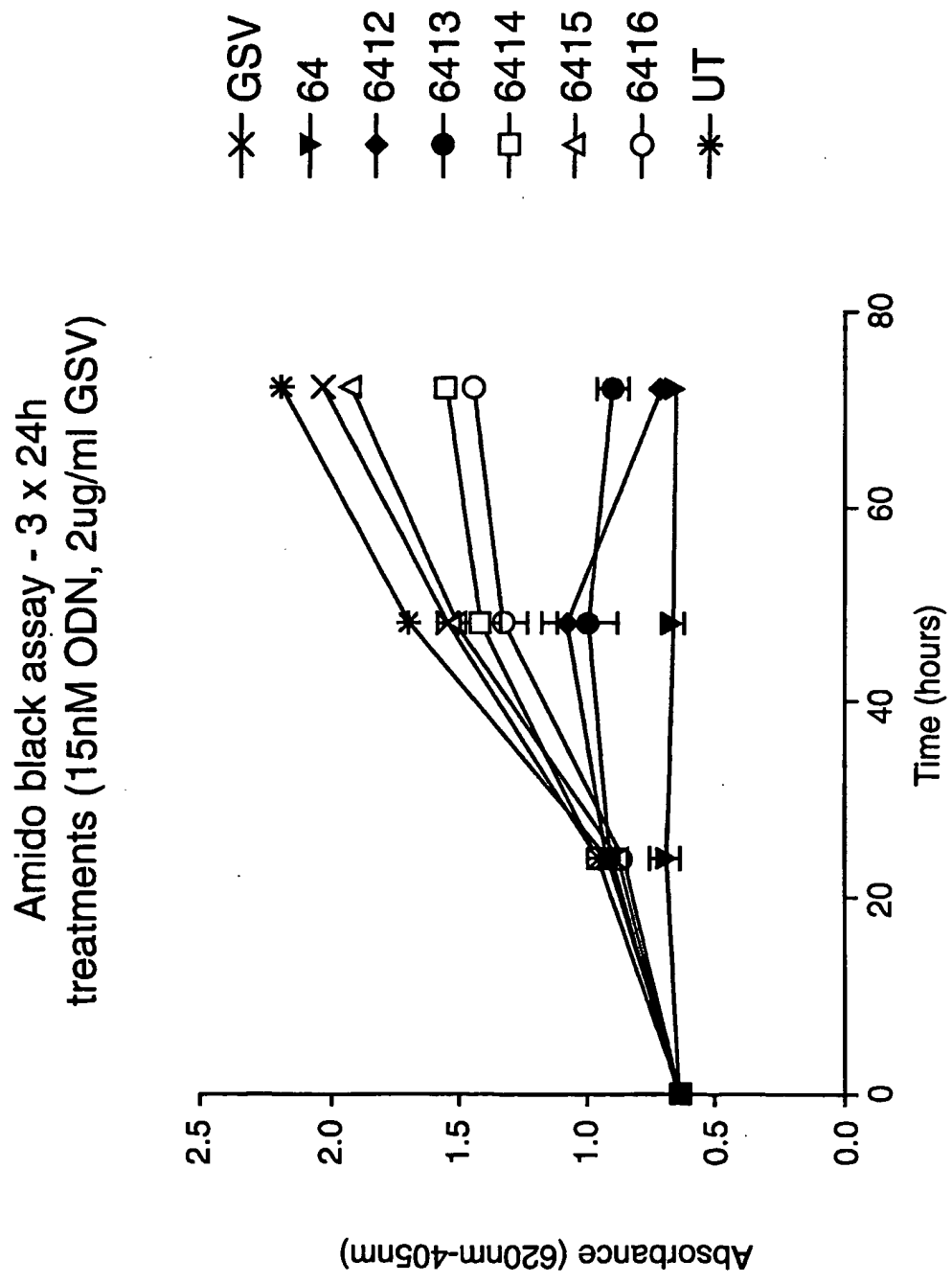

Amido black assay - 3 x 24h
treatments (15nM ODN, 2ug/ml GSV)
GSV
64
6412
6413
6414
6415
6416
UT
Absorbance (620nm-405nm)
2.5
2.0
1.5
1.0
0.5
0.0
0
20
40
60
80
Time (hours)

Figure 35

SEQUENCE LISTING

<110> MURDOCH CHILDREN'S RESEARCH INSTITUTE

<120> A METHOD FOR THE PROPHYLAXIS AND/OR TREATMENT OF MEDICAL DISORDERS

<130> 2288267/EJH

<140> INTERNATIONAL
<141> 2000-06-21

<150> 60/140345
<151> 1999-06-21

<160> 24

<170> PatentIn Ver. 2.1

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<211> 1433
<212> DNA
<213> synthetic construct

<400> 1
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ctgccgagag tgggctgccc cgcgctgccg ctgccgccgc cgccgctgct gccgctgctg 180
ccgctgctgc tgctgctact gggcgcgagt ggcggcggcg gcggggcgcg cgcggaggtg 240
ctgttccgct gcccgccctg cacacccgag cgcctggccg cctgcgggcc cccgccggtt 300
gcgccgcccg ccgcggtggc cgcagtggcc ggaggcgccc gcatgccatg cgcggagctc 360
gtccgggagc cgggctgcgg ctgctgctcg gtgtgcgccc ggctggaggg cgaggcgtgc 420
ggcgtctaca ccccgcgctg cggccagggg ctgcgctgct atccccaccc gggctccgag 480
ctgcccctgc aggcgctggt catgggcgag ggcacttgtg agaagcgccg ggacgccgag 540
tatggcgcca gcccggagca ggttgcagac aatggcgatg accactcaga aggaggcctg 600
gtggagaacc acgtggacag caccatgaac atgttgggcg ggggaggcag tgctggccgg 660
aagcccctca agtcgggtat gaaggagctg gccgtgttcc gggagaaggt cactgagcag 720
caccggcaga tgggcaaggg tggcaagcat caccttggcc tggaggagcc caagaagctg 780
cgaccacccc ctgccaggac tccctgccaa caggaactgg accaggtcct ggagcggatc 840
tccaccatgc gccttccgga tgagcggggc cctctggagc acctctactc cctgcacatc 900

cccaactgtg acaagcatgg cctgtacaac ctcaaacagt gcaagatgtc tctgaacggg 960
cagcgtgggg agtgctggtg tgtgaacccc aacaccggga agctgatcca gggagccccc 1020
accatccggg gggaccccga gtgtcatctc ttctacaatg agcagcagga ggcttgcggg 1080
gtgcacaccc agcggatgca gtagaccgca gccagccggt gcctggcgcc cctgcccccc 1140
gcccctctcc aaacaccggc agaaaacgga gagtgcttgg gtggtgggtg ctggaggatt 1200
ttccagttct gacacacgta tttatatttg gaaagagacc agcaccgagc tcggcacctc 1260
cccggcctct ctcttcccag ctgcagatgc cacacctgct ccttcttgct ttccccgggg 1320
gaggaagggg gttgtggtcg gggagctggg gtacaggttt ggggaggggg aagagaaatt 1380
tttatttttg aacccctgtg tccctttttgc ataagattaa aggaaggaaa agt 1433

<210> 2
<211> 2474
<212> DNA
<213> synthetic construct

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 00/00693

**A. CLASSIFICATION OF SUBJECT MATTER**

Int Cl[7]: A61K 38/30; 17/06; 17/02

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Derwent WPAT IGF-1, IGFBP, Insulin Like Growth Factor/Binding Pair.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | AU 77314/94,A (688793) (Celtrix Pharmaceuticals, Inc.) 30 March 1995. | 1-9, 20-22, 25, 29-37 |
| X | AU 28753/95,A (692278) (Royal Children's Hospital Research Foundation, Australia.) 25 January 1996. | 1-13, 20-23, 29-36 |
| X | Wraight, Christopher J. et al., Expression of insulin-like growth factor binding protein-3 (IGFBP-3) J. Invest. Dermatol. (1997), 108(4), 452-456. | 1-13,20-23,29-36 |

[X] Further documents are listed in the continuation of Box C

[ ] See patent family annex

* Special categories of cited documents:

"A" Document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 24 August 2000 | -4 OCT 2000 |

| Name and mailing address of the ISA/AU | Authorized officer |
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| AUSTRALIAN PATENT OFFICE<br>PO BOX 200<br>WODEN ACT 2606 AUSTRALIA<br>E-mail address: pct@ipaustralia.gov.au<br>Facsimile No.: (02) 6285 3929 | A. WILCOX<br>Telephone No.: (02) 6283 2243 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 00/00693

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | Jeschke, Marc G.; Barrow, Robert E.; Hawkins, Hal K.; Chrysopoula, Mina S. T.; Perez-Polo, J. Regina; Herdon, David, N. Effect of Multiple gene transfers of insulin like growth factor I complementary DNA gene constructs in rats after thermal injury. Arch. Surg. (1999), 134(10), 1137-1141. | 1-13,20-23,29-36 |
| X | WO 96/01636 (Royal Childrens Hospital Research Foundation) 25 January 1996. | 1-13 |
| X | WO 96/33216 (Pharmacia AB) 24 October 1996. | 1-13 |

# INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 00/00693

**Box I** **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,2,5-8 have been partially searched.
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The specification provides support for methods and compositions which inhibit IGF-1 mediated cell proliferation and/or inflammation. There is no basis in the specification for methods and compositions derived from an invention for the treatment of cell proliferation and/or inflammation mediated by factors other than IGF-1.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

**Box II** **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:
The claims are directed to methods and compositions which inhibit IGF-1 mediated cell proliferation and/or inflammation. The broader claims include cell proliferation and/or inflammation mediated by keratinocyte growth factor (KGF), TGF-α, TNF-α, IL-1, IL-2, IL-6, IL-8 and/or basic fibroblast growth factor (bFGF). Claims 1,2 and 5-8 are considered to include multiple inventions.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.